

EXHIBIT A

Sirolimus: A new agent for prevention of renal allograft rejection

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The widespread growth and success of transplantation are attributed to the introduction of the immunosuppressive agent cyclosporine into clinical practice in the late 1970s. Current one-year graft survival rates among renal allograft recipients are about 90%. Despite the success of cyclosporine-based therapy, the use of this agent has been complicated by the numerous toxicities associated with it, in particular, nephrotoxicity. Moreover, the immunosuppressive tacrolimus, introduced into clinical practice more recently, also is associated with significant nephrotoxicity. As a result, research efforts in the area of transplantation have been directed toward identifying a potent and selective immunosuppressive agent that has fewer adverse effects associated with it.

Over the past few years, several new immunosuppressants have been approved for clinical use in solid or-

Abstract: The pharmacology, pharmacokinetics, clinical efficacy, adverse effects, and dosage and administration of sirolimus are reviewed.

Sirolimus can be used as an adjunct to cyclosporine and corticosteroids for preventing organ rejection in renal allograft recipients. It appears to block cell-cycle progression in the mid-to-late G₁ phase; it also inhibits interleukin-2-dependent and independent proliferation of B-lymphocytes and production of immunoglobulins A, M, and G. Sirolimus is extensively metabolized by the liver and undergoes O-demethylation and hydroxylation. The mean oral clearance is $208 \pm 95 \text{ mL}/\text{hr}/\text{kg}$ with an elimination half-life of 57 to 63 hours in kidney transplant recipients. Sirolimus is poorly absorbed from the gastrointestinal tract; its apparent oral bioavailability is about 15%. Two pivotal Phase III, multicenter, randomized, double-blind trials evaluating the efficacy of sirolimus in the prophylaxis of acute renal allograft rejection after transplantation have been conducted. A significant reduction in the occurrence of acute rejection was noted in both trials compared with az-

athioprine- or placebo-treated patients. Also, both sirolimus groups required significantly less antibody therapy for treatment of rejection. The primary adverse effects associated with sirolimus therapy include hypercholesterolemia and hypertriglyceridemia. Hypertension, diarrhea, increased creatinine, hypokalemia, arthralgia, rash, acne, leukopenia, and thrombocytopenia have also been observed. The labeled recommendations are a 6-mg loading dose as soon as possible after transplantation and a maintenance dose of 2 mg per day.

Sirolimus is a potent novel immunosuppressive agent with proven efficacy in the prevention of acute rejection after renal transplantation. Use of sirolimus may lead to effective therapeutic strategies for sparing the use of cyclosporine and corticosteroids.

Index terms: Dosage; Drug interactions; Graft rejection; Immunosuppressive agents; Mechanism of action; Pharmacokinetics; Sirolimus; Toxicity; Transplantation
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gan transplantation, resulting in significant reductions in the occurrence of acute rejection. Sirolimus is the newest immunosuppressive agent to be introduced and shows promise as an adjunctive immunosuppressive agent. The drug is a macrocyclic triene antibiotic produced by the actinomycete *Streptomyces hygroscopicus*. It was isolated from a soil sample collected in Rapa Nui, commonly known as Easter Island.¹ Although sirolimus was originally isolated for its antifungal properties, its clinical development for use in transplantation has evolved because of its unique mechanism of action and apparent efficacy in prolonging allograft survival in various animal models.^{2,3} Adverse events associated with the use of sirolimus include the development of hypertriglyceridemia, hypercholesterolemia, thrombocytopenia, leukopenia, and an increase in serum creatinine.⁴

In vitro and *in vivo* studies have documented the potent immunosuppressive activity of sirolimus, and hence this agent was developed to prevent allograft rejection in organ transplantation.⁵⁻¹⁰ It inhibits T- and B-cell proliferation by blocking signals from cytokines, such as interleukin-2 (IL-2) and IL-4.⁵⁻⁷ Unlike cyclosporine and tacrolimus, sirolimus does not affect the calcineurin pathway.

In vitro and *in vivo* studies also have demonstrated that both sirolimus and cyclosporine exhibit a synergistic immunosuppressive effect when used together.⁸⁻¹⁰ It is hoped that the improved efficacy exhibited by this new immunosuppressive combination will allow for sparing of cyclosporine and corticosteroids,

thereby minimizing some of the chronic toxicities associated with these agents.

Product description

Sirolimus (formerly known as rapamycin, Rapamune, Wyeth-Ayerst Laboratories, Radnor, PA) is a macrolide antibiotic isolated from the actinomycete *Streptomyces hygroscopicus*.

Pharmacology

A hydrophobic molecule with a molecular weight of 914.2, sirolimus is a 31-membered macrocyclic lactone with a hemiketal masked α - and β -diketo amide moiety (similar to tacrolimus) with a ring structure that contains a unique triene segment.¹

Sirolimus has been shown to inhibit T-lymphocyte proliferation through its various component antigens utilizing calcium-dependent or calcium-independent pathways.¹⁰ Reported concentrations causing 50% inhibition of T-lymphocyte proliferation vary and range from 0.1 to 300 nM.¹⁰ Sirolimus appears to block cell-cycle progression in the mid-to-late G₁ phase, as T-cell proliferation is still inhibited when sirolimus is added up to 24 hours after cell stimulation.⁹ In contrast, cyclosporine and tacrolimus are ineffective in inhibiting T-cell proliferation when added after T-cell activation.⁹ These *in vitro* studies support the hypothesis that, unlike cyclosporine and tacrolimus, which block calcium-dependent cytokine transcription early in the G₁ phase, sirolimus inhibits cytokine-mediated signal transduction pathways later in the G₁ phase. It also inhibits IL-2-

dependent and independent proliferation of B-lymphocytes and production of immunoglobulin A, immunoglobulin M, and immunoglobulin G.⁶ These latter effects on the production of antibodies are believed to contribute to the immunomodulating effects of this agent.

Like cyclosporine and tacrolimus, sirolimus binds to cytosolic receptors known as immunophilins. Cyclosporine binds to the cyclophilin class of immunophilins, whereas both tacrolimus (FK 506) and sirolimus (which exhibit structural similarities) bind to the immunophilins known as FK 506 binding proteins (FKBPs). The role of immunophilins is not well understood; however, it appears that the complexes formed by cyclosporine and tacrolimus with their respective immunophilins inhibit the formation of calcineurin, a calcium-calmodulin-dependent serine and threonine phosphatase. The inhibition of calcineurin activity prevents the dephosphorylation of the nuclear factor of activated T-cells (NF-AT) cytoplasmic subunit, which is necessary for the NF-AT to migrate to the nucleus, where it binds to the IL-2 promoter sequence. The inhibition of calcineurin mitigates the production of IL-2 and other cytokines, thereby blocking their early activation of T cells in the G₀ and G₁ phases.

In contrast, the sirolimus and FKBP complex binds to the mammalian target of rapamycin (mTOR). Binding of the sirolimus and FKBP complex to mTOR inhibits IL-2-mediated signal transduction pathways that prevent cell-cycle progression from the G₁ phase to the S phase.^{5,11} The sirolimus-FKBP complex inhibits the phosphorylation necessary for activation of the 70-kDa, S6 (p70^{6k}) protein kinase, which is responsible for protein synthesis and progression of T cells from the G₁ phase into the S phase.¹¹ Thus, while cyclosporine and tacrolimus work to inhibit production of cytokines, such as IL-2, IL-3, IL-4, granulocyte-macrophage

colony-stimulating factor, and tumor necrosis factor, sirolimus appears to inhibit the response to these cytokines, eliciting its effects at a later stage. Antagonistic interactions between tacrolimus and sirolimus in vitro have led many to suggest that the two agents could not be used together in clinical practice because of competition in binding to FKBP.¹² Limited in vivo data suggest, however, that they may be used together without antagonistic effects.¹³ Further studies are needed to determine whether the agents can be used concomitantly in humans without compromising clinical efficacy.

Sirolimus also appears to inhibit proliferation of nonlymphoid tumor cells and smooth muscle cell proliferation in response to basic fibroblast growth factor and platelet-derived growth factor.¹⁴ These effects on smooth muscle cell proliferation have led to studies examining the effect of the agent in a model of allograft vascular rejection in rats. Preliminary data suggest that sirolimus can inhibit the vascular response to injury caused by allograft rejection.¹⁵ Moreover, in vivo studies suggest that sirolimus can reduce arterial intimal thickening.¹⁶ This direct antiproliferative effect on smooth muscle cell proliferation has generated interest in this agent for preventing the arterial intimal thickening associated with chronic rejection.

While current clinical trials have mainly focused on the efficacy of sirolimus in preventing acute rejection in renal allograft recipients, clinical trials in other solid organ transplant populations are also being conducted for both prevention and treatment of refractory rejection. Animal studies that are examining the efficacy of sirolimus in various autoimmune diseases, including systemic lupus erythematosus, insulin-dependent diabetes mellitus, collagen-induced arthritis, and multiple sclerosis, are also currently underway. Preliminary evidence suggests

that sirolimus may delay the onset or worsening of these diseases in animal models and holds promise for treating these and other autoimmune disorders.

Pharmacokinetics

The pharmacokinetic characteristics of sirolimus have not been well described, and most of the data have been derived from renal allograft recipients. Preliminary data suggest that sirolimus exhibits much of the same pharmacokinetic variability that is evident with cyclosporine and tacrolimus. Because of the limited pharmacokinetic data available, additional multidose studies of various transplant populations are required to further clarify the pharmacokinetic characteristics of sirolimus and how these characteristics may be affected by age, sex, race, and renal or hepatic dysfunction. To this end, clinical trials in humans are continuing.

Absorption and distribution. Sirolimus is poorly absorbed from the gastrointestinal tract. Its apparent oral bioavailability is reported to be about 15%.¹⁷ The drug is rapidly absorbed, with peak concentration times ranging from 0.7 to 3 hours. The time to achieve maximum blood concentration (t_{max}) is reported to be 1.42 ± 1.20 hours.¹⁸ In an ascending-dose, Phase I pharmacokinetic study conducted in renal transplant patients ($n = 40$), whole-blood trough concentrations (range of means, 5.1–101 ng/mL) correlated well with the area under the blood concentration-time curve (AUC; range of means, 70.2–1428 ng·hr/mL).¹⁸ These findings suggest that sirolimus blood trough concentrations will be a useful tool for assessing drug exposure. Doses in this study ranged from 0.5 to 6.5 mg/m² and were administered every 12 hours, and the corresponding mean peak blood concentrations of sirolimus ranged from 10 to 210 ng/mL. In a randomized, double-blind, placebo-controlled, Phase II trial among renal allograft recipients

($n = 12$), whole-blood peak concentrations and AUCs correlated with the oral dose in the dosage range of 5 to 15 mg/m².¹⁹ The maximum blood concentration (C_{max}) values were quite variable and ranged from 14 ng/mL to 210 ng/mL following oral doses ranging from 3 mg/m² to 15 mg/m² (Table 1).¹⁹

Preliminary evidence suggests that African-American patients exhibit a reduced rate and extent of absorption of sirolimus. Pharmacokinetic parameters were compared among African-American transplant patients ($n = 9$) and transplant patients who were not African-American ($n = 17$). The reported t_{max} was 2.03 ± 1.72 hours in African-Americans versus 1.06 ± 0.57 hours in non-African-American recipients ($p = 0.04$).¹⁸ With respect to oral absorption, no pharmacokinetic differences have been observed between male and female patients.¹⁸ The effect of a high-fat diet on sirolimus absorption has not been well characterized; preliminary evidence suggests that a high-fat diet may prolong the absorption time and increase the AUC.⁴ Some pharmacokinetic values of sirolimus in stable renal allograft recipients are delineated in Table 2.

Sirolimus is extensively distributed into tissues. The apparent volume of distribution is large and variable, ranging from 5.6 to 16.7 L/kg in stable renal allograft recipients. The mean volume of distribution following oral administration in stable renal transplant patients is 12 ± 4.6 L.

Table 1.
Maximum Blood Concentrations after Ascending Doses in Stable Renal Transplant Patients^a

Sirolimus Dose (mg/m ²)	Maximum Blood Concentration (ng/mL)
3	49–129
5	14–80
10	80–183
15	177–210

^aAdapted from reference 19.

Table 2.

Steady-State Pharmacokinetic Values in Stable Renal Transplant Patients Participating in Phase III Clinical Trials^{a,b}

Dosage	<i>n</i>	<i>C</i> _{max} (ng/mL) ^c	<i>t</i> _{max} (hr)	AUC (ng·hr/mL) ^c	CL/F/WT (mL/hr/kg)
2 mg	19	12.2 ± 6.2	3.01 ± 2.4	158 ± 70	182 ± 72
5 mg	23	37.4 ± 21	1.84 ± 1.3	396 ± 193	221 ± 143

^aTable adapted from reference 4. Multiple-dose study, with sirolimus administered four hours after cyclosporine; values are presented as mean ± standard deviation.

^bData represent pharmacokinetic analysis performed at months 1, 3, and 6 after transplant. There were no differences reported with respect to treatment group or month.

^c*C*_{max} = peak blood concentration, *t*_{max} = time to peak concentration, AUC = total area under the curve, CL/F/WT = oral clearance.

^dDosage normalized.

kg.¹⁸ Partitioning between blood and plasma is extensive and also varies widely among patients.¹⁸ The mean blood-to-plasma ratio of sirolimus in stable renal allograft recipients is 36 ± 17.9 .⁴ The whole-blood-to-plasma ratio does not appear to be temperature or concentration dependent. Sirolimus is primarily bound to red blood cells (95%). Distribution among the other cellular components is 3% plasma, 1% lymphocytes, and 1% granulocytes.²⁰ In the plasma, sirolimus is extensively bound to plasma proteins (92%) including serum albumin (97%), α_1 -acid glycoprotein, and lipoproteins.⁴ The distribution of sirolimus appears to be influenced by body weight and body surface area.²¹

Elimination and metabolism. Sirolimus is extensively metabolized by the liver and undergoes *O*-demethylation and hydroxylation. Cytochrome P450 3A4 is the major metabolizing isoenzyme for this agent.²² Metabolites are excreted primarily via the bile in the feces. Only 2.2% of the drug or its metabolites are renally eliminated.⁴ Seven metabolites of sirolimus have been identified in humans and exhibit less than 10% of the immunosuppressive activity of the parent drug.^{4,23} Approximately 10 metabolites have been identified in animal studies, but their immunosuppressive activity has yet to be established.²⁴ Large intersubject variability occurs in the oral clearance of sirolimus. The mean oral clearance is 208 ± 95 mL/hr/kg with an elimination half-life of 57 to 63 hours in kidney transplant recipi-

ents.¹⁸ Oral clearance of sirolimus is lower among males than females (72.3 hours versus 61.3 hours); however, there are no dosage-adjustment recommendations based on these differences in clearance.⁴ Oral clearance among black recipients has been reported to be 45% higher compared with nonblack patients, 260 ± 91 mL/hr/kg versus 180 ± 87 mL/hr/kg, respectively ($p = 0.04$).¹⁸ However, in the Phase III trials no differences were observed in mean blood trough concentrations between blacks (*n* = 139) and non-blacks (*n* = 724).⁴ Limited pharmacokinetic studies have been performed in the pediatric population. Clearance of sirolimus appears to be much higher in the pediatric patient when compared with adult patients.⁴

Special populations. Renal impairment. As sirolimus is not extensively eliminated via the kidneys, renal dysfunction should have little effect on sirolimus or sirolimus-metabolite concentrations.⁴ The effect of dialysis treatments on blood trough concentrations of sirolimus has not been established. Because of the lipophilic nature of this agent, it is not likely to be effectively removed by dialytic therapy.

Hepatic impairment. Sirolimus (15 mg) was administered to 18 healthy volunteers and to 18 patients with Child-Pugh classification A or B hepatic impairment.⁴ The reported mean AUC in patients with hepatic disease was 1567 ± 616 ng·hr/mL versus 970 ± 272 ng·hr/mL in patients with normal hepatic function. Hepatic disease does not appear to

alter the absorption of sirolimus. The reported *C*_{max} and *t*_{max} were similar in both groups. The oral clearance of sirolimus was significantly decreased (144 ± 62 mL/hr/kg versus 215 ± 76 mL/hr/kg). The mean *t*_{1/2} was increased in patients with hepatic impairment: 113 ± 41 hours versus 79 ± 12 hours in subjects with normal hepatic function.

Therapeutic drug monitoring. Routine drug-level monitoring is currently not recommended for most patients. Sirolimus blood trough concentrations should be monitored in those patients who exhibit altered pharmacokinetic characteristics (including patients with hepatic impairment, children, and African-Americans) and during concurrent administration of agents that are metabolized via cytochrome P450 3A4 or act as substrates for *p*-glycoprotein and for patients who are taking relatively low doses of cyclosporine or for whom cyclosporine has been discontinued. Limited in vivo data suggest that blood trough concentrations between 10 to 15 ng/mL during the initial months after renal transplantation are associated with favorable outcomes.²⁵ The pivotal Phase III clinical trials featured the use of fixed dosages of sirolimus. While routine monitoring of sirolimus blood trough concentrations for dosage titration was not performed, blood trough concentrations of sirolimus were obtained for subsequent analysis. Mean whole-blood sirolimus trough concentrations for the 2-mg dose (*n* = 226) and the 5-mg dose (*n* = 219) were reported as

8.59 ± 4.0 ng/mL and 17.3 ± 7.4 ng/mL, respectively.⁴ In addition, whole-blood trough concentrations were found to correlate well with AUC, suggesting that monitoring of sirolimus blood trough concentrations will be a useful tool for assessing total drug exposure. Whether therapeutic drug monitoring for sirolimus in the future will involve blood trough concentration monitoring or pharmacodynamic monitoring, such as measuring activity of p70⁵⁶ kinase (the enzyme responsible for cell-cycle progression from the G₁ phase through the S phase) in lymphocytes, remains to be established. Precise guidelines for therapeutic drug monitoring of sirolimus remain to be developed.

Whole blood is the preferred matrix for measuring sirolimus concentrations because of the relative distribution of sirolimus in the red blood cell. Whole-blood trough concentrations of sirolimus should be measured immediately before the administration of the scheduled dose of sirolimus. Whole-blood trough samples should be collected in ethylenediaminetetraacetic acid tubes and protected from light. High-performance liquid chromatography (HPLC) and HPLC-mass spectroscopy are the preferred assays for determining sirolimus blood concentrations. An immunoassay is currently under development.

Indications

Sirolimus is indicated for use as an adjunct to cyclosporine and

corticosteroids for preventing organ rejection in renal allograft recipients.

Clinical efficacy

Two pivotal Phase III, multicenter, randomized, double-blind trials evaluating the efficacy of sirolimus in the prophylaxis of acute renal allograft rejection after transplantation have been conducted. The Rapamune U.S. Multicenter Study²⁶ (Table 3) and the Rapamune Global Study Group²⁷ (Table 4) were the two main Phase III studies performed. Six-month data from these pivotal trials were submitted to FDA to gain approval for this agent. Some 80 centers worldwide participated in these two trials and had a combined enrollment of 1295 patients. The results of these studies have established the efficacy of sirolimus in preventing acute rejection after renal transplantation. A significant reduction in the occurrence of acute rejection was noted in both trials compared with azathioprine- or placebo-treated patients. The primary outcome measure in these studies was the composite incidence of biopsy-proven acute rejection, graft loss, or patient death within the first six months after transplantation.

Very little has been published regarding the clinical efficacy and safety of sirolimus. Most of the data presented in this monograph are derived from scientific abstracts and the package insert, which contain very limited information. Published data are forthcoming.

In the Phase III Multicenter U.S.

study, 719 recipients of primary mismatched cadaveric or living-donor renal allografts were randomly assigned to one of three treatment groups in a 2:2:1 distribution within 24 to 48 hours posttransplant.²⁶ Patients were stratified at the time of randomization by center and race (23% African-American, 77% non-African-American). The study groups comprised 284 patients randomized to receive sirolimus 2 mg/day, 274 patients randomized to receive sirolimus 5 mg/day, and 161 patients randomized to receive azathioprine 2 to 3 mg/kg/day. Antibody induction therapy was prohibited by protocol. Baseline immunosuppressive therapy consisted of cyclosporine and prednisone. Cyclosporine doses were titrated to maintain targeted blood trough levels, which represented usual clinical practice. Both of the sirolimus regimens were significantly more effective than azathioprine in reducing the incidence of acute rejection. The primary composite endpoint (incidence of acute rejection, graft loss, and death) was also significantly better among those patients treated with sirolimus (Table 3). Moreover, both sirolimus groups required significantly less antibody therapy (muromonab-CD3 or antithymocyte globulin) for treatment of rejection. Six- and 12-month graft and patient survival did not differ among treatment groups.²⁶ When the rates of rejection are stratified by race, preliminary evidence suggests that African-Americans tend to have more favorable results with the 5-mg dose of sirolimus versus the 2-

Table 3.

Results of U.S. Multicenter Phase III Clinical Trial with Sirolimus in Renal Transplantation^a

Variable	Sirolimus 2 mg (n = 284)	Sirolimus 5 mg (n = 274)	Azathioprine (n = 161)	P
Composite endpoint ^b at 6 mo	18.7%	16.8%	32.3%	<0.05 ^c
Acute rejection at 6 mo	16.5%	11.3%	29.2%	<0.05 ^c
Graft survival at 6 mo	98.9%	97.1%	97.5%	>0.05
Patient survival at 6 mo	99.3%	98.2%	100%	>0.05
Graft survival at 12 mo	94.7%	92.7%	94.0%	>0.05
Patient survival at 12 mo	97.2%	96.0%	98.1%	>0.05

^aData derived from reference 4.

^bPrimary composite efficacy endpoint includes first occurrence of biopsy-proven acute rejection, graft loss, or death during the first six months after transplantation.

^cp < 0.05 azathioprine versus sirolimus 2 mg and sirolimus 5 mg.

Table 4.

Results of the Rapamune Global Study in Renal Transplantation^a

Variable	Sirolimus 2 mg (n = 227)	Sirolimus 5 mg (n = 219)	Placebo (n = 130)	p
Composite endpoint ^b at 6 mo	30.0%	25.6%	47.7%	<0.05 ^c
Acute rejection at 6 mo	24.7%	19.2%	41.5%	<0.05 ^c
Graft survival at 6 mo	96.9%	96.3%	96.1%	>0.05
Patient survival at 6 mo	97.8%	97.3%	97.7%	>0.05
Graft survival at 12 mo	89.9%	90.9%	87.7%	>0.05
Patient survival at 12 mo	96.5%	95.0%	94.6%	>0.05

^aData derived from reference 4.^bPrimary composite efficacy endpoint includes first occurrence of biopsy-proven acute rejection, graft loss, or death during the first six months after transplantation.^cp < 0.05 placebo versus sirolimus 2 mg and sirolimus 5 mg.

Table 5.

Comparison of Failure Rates by Race^{a,b}

Race	U.S. Study Sirolimus 2 mg	U.S. Study Sirolimus 5 mg	U.S. Study Azathioprine	Global Study Sirolimus 2 mg	Global Study Sirolimus 5 mg	Global Study Placebo
Black	34.9% (n = 63)	18.0% (n = 61)	33.3% (n = 42)	30.8% (n = 26)	33.7% (n = 27)	38.5% (n = 130)
Nonblack	14.0% (n = 221)	16.4% (n = 213)	31.9% (n = 119)	29.9% (n = 201)	24.5% (n = 192)	48.7% (n = 117)

^aFailure rate at 6 mo.^bAdapted from reference 4.mg dose (Table 5).⁴

In the Phase III Global Multicenter study (Australia, Canada, Europe, United States), 576 primary mismatched cadaveric or living-related donor allograft recipients were randomized to one of three treatment groups in a 2:2:1 ratio.²⁷ The study population comprised 227 patients who received sirolimus 2 mg/day, 219 patients who received sirolimus 5 mg/day, and 130 placebo-treated patients. Similar to the U.S. study, maintenance immunosuppression consisted of cyclosporine and prednisone. Cyclosporine doses were titrated to maintain targeted blood trough levels, which represented usual clinical practice. Antibody induction therapy was prohibited. As in the U.S. study, both sirolimus regimens were more effective than placebo in reducing the acute rejection and improving the composite endpoint (incidence of acute rejection, graft loss, and death) within the first six months of transplant (Table 4). Also, the need for antibody therapy for treating organ rejection tended to be lower in both of the sirolimus groups; however, the difference in antibody requirements was signifi-

cant only in the 2-mg/day group when compared with placebo. Graft and patient survival were similar in all treatment groups.²⁷

Other clinical trials

Cyclosporine-sparing protocols. In an open-label, parallel group, European Multicenter Phase II study (11 centers in Sweden, France, Spain, and the United Kingdom), cyclosporine-based therapy was compared with sirolimus-based therapy for primary immunosuppression.²⁸ Baseline immunosuppression consisted of azathioprine and corticosteroids. Some 41 patients were randomly treated with sirolimus, and 42 patients were treated with cyclosporine. Cyclosporine and sirolimus doses were titrated based on levels; however, targeted levels were not noted in the abstract. The incidence of acute rejection was similar in both groups (41% in the sirolimus group, and 38% in the cyclosporine group [$p > 0.05$]). One-year graft survival was higher in the group that received sirolimus (98% versus 90%); however, these differences were not statistically significant. One-year patient survival was 100% in sirolimus-

treated patients versus 98% in cyclosporine-treated patients.

A randomized, Phase IIb, multicenter trial evaluated the potential cyclosporine-sparing effects of sirolimus.²⁹ The cyclosporine group, given a full dose, received full-dose cyclosporine added to placebo or doses of sirolimus of 1 to 3 mg/m²/day. The patients who received reduced doses of cyclosporine received sirolimus in doses of 1, 3, or 5 mg/m²/day. The dose of cyclosporine used in this study was not specified in the abstract. All patients received tapering doses of corticosteroids. The incidence of acute rejection was significantly reduced among patients treated with full-dose cyclosporine and sirolimus compared to those receiving full-dose cyclosporine and placebo (11% versus 40%, respectively, $p < 0.05$). No clinically significant differences were reported in the rates of acute rejection in patients who received reduced-dose cyclosporine and sirolimus and those who received full-dose cyclosporine and placebo. An analysis of the subset, however, revealed a 13% incidence of rejection among non-African-American renal allograft recipients

versus a 56% incidence in African-Americans ($p < 0.05$). African-American patients who received full-dose cyclosporine and sirolimus had significantly lower rates of acute rejection than those who received reduced doses of cyclosporine and sirolimus (10% versus 56%, $p = 0.021$). These results were attributed to the relatively low oral bioavailability and rapid systemic clearance of cyclosporine among this group. Cyclosporine blood trough concentrations among African-Americans who experienced acute rejection were lower compared with those who did not experience rejection. Mean blood trough concentrations at months 1, 3, and 6 for patients who experienced rejection were 182, 177, and 177 ng/mL, respectively, compared with 266, 242, and 246 ng/mL among those who did not experience rejection. This reduced-dose strategy remains to be studied in a concentration-controlled fashion across all racial groups.

Treatment of refractory rejection. Kahan et al.³⁰ have reported on the beneficial effect of sirolimus in reversing refractory allograft rejection (rejection refractory to conventional antirejection agents) in cyclosporine-treated patients. In a cohort of cyclosporine-treated renal transplant patients ($n = 13$) with refractory rejection, 70% of rejection epi-

sodes were reversed with sirolimus therapy. Sirolimus was initiated at 7 mg/m² for five days. Thereafter, patients were maintained on a dose of 5 mg/m². Patients were maintained on their pre-existing cyclosporine dose, and corticosteroids were withdrawn or tapered as tolerated. Corticosteroid treatments for five patients were completely tapered off.³⁰ Large, well-controlled studies are needed to validate these findings.

Corticosteroid withdrawal protocols. Most of the preliminary data reported thus far indicate that the addition of sirolimus to cyclosporine-based therapy allows for corticosteroid withdrawal in patients at low risk for acute rejection. In a study designed to assess the risks associated with withdrawal of corticosteroids in patients who receive sirolimus, corticosteroid withdrawal was accomplished in about 70% of patients.³¹ The study population involved 75 patients who had been maintained on cyclosporine, prednisone, and sirolimus from the time of transplantation. Corticosteroid withdrawal was attempted at or one month after transplantation if the patient had not experienced an episode of acute rejection or did not exhibit a medical contraindication to steroid withdrawal. Of those eligible for corticosteroid withdrawal ($n = 60$), 25 patients were recipients of

human leukocyte antigen-mismatched living-donor kidneys, and 35 patients were cadaver-donor recipients. At one year, 77% of living-donor recipients were steroid free compared with 70% of cadaver recipients. There were two living-related recipients who experienced an episode of acute rejection. After six months of steroid therapy, these patients were successfully taken off corticosteroids. Among the cadaver recipients, four patients (15%) experienced an acute rejection episode, and four (15%) had corticosteroid treatment reinitiated secondary to various medical conditions. Only 70% remained off of steroids at 12 months. No clinically significant differences in laboratory variables, such as serum triglycerides, serum cholesterol, and white blood cell counts, were noted in either group.

Adverse effects and toxicities

The primary adverse effects associated with sirolimus therapy in the two Phase III trials were mild dose-related thrombocytopenia and increases in serum triglycerides and serum cholesterol values (Table 6).^{4,32} Sirolimus's propensity to increase serum lipids is its most bothersome adverse effect. The severity of hypertriglyceridemia is generally greater than the hypercholesterolemia observed. Although lipid dis-

Table 6.

Common Adverse Events Associated with Sirolimus Therapy in the Phase III Trials

Adverse Event	Sirolimus 2 mg U.S. Study ($n = 281$)	Sirolimus 2 mg Global Study ($n = 218$)	Sirolimus 5 mg U.S. Study ($n = 269$)	Sirolimus 5 mg Global Study ($n = 208$)	Azathioprine U.S. Study ($n = 160$)	Placebo Global Study ($n = 124$)
Hypertension	43%	45%	39%	49%	29%	48%
Diarrhea	32%	25%	42%	35%	28%	27%
Increased creatinine	35%	39%	37%	40%	28%	38%
Hypokalemia	17%	11%	21%	17%	11%	9%
Arthralgia	25%	25%	27%	31%	21%	18%
Rash	12%	10%	13%	20%	6%	6%
Acne	31%	22%	20%	30%	23%	30%
Thrombocytopenia	13%	14%	20%	30%	9%	9%
Leukopenia	9%	9%	15%	13%	20%	8%
Hypercholesterolemia	38%	43%	42%	46%	33%	23%
Hyperlipidemia	38%	45%	44%	57%	28%	23%

*Data derived from reference 4.

orders are a well-known adverse effect of cyclosporine, occurring in about 30% to 50% of patients, the addition of sirolimus appears to increase the risk for development of these disorders.³² Treatment with lipid-lowering agents was required in 42% to 52% of patients randomized to sirolimus in the Phase III trials compared with 22% of patients receiving azathioprine and 16% of patients receiving placebo.⁴ Hydroxymethyl glutaryl-coenzyme A (HMG-CoA)-reductase inhibitors and fibrin acid derivatives were used in many cases for management of these lipid disorders and appeared to be well tolerated.⁴ The temporary cessation or reduction of sirolimus dosages may be necessary in some cases to control elevations in serum lipids.³²

An unanticipated adverse event associated with the use of sirolimus in the Phase III trials was an increase in serum creatinine among patients receiving sirolimus.⁴ Patients treated with cyclosporine and sirolimus in the Phase III trials had higher serum creatinine values and lower glomerular filtration rates at one year when compared with patients treated with cyclosporine in conjunction with azathioprine or placebo. The mean glomerular filtration rate among patients receiving the 2-mg dose of sirolimus in the U.S. study was 57.4 mL/min compared with 65.9 mL/min among patients receiving azathioprine. In the European study the mean glomerular filtration rate was 54.9 mL/min among patients receiving the 2-mg dose of sirolimus versus 61.7 mL/min among patients receiving placebo. Among patients receiving the 5-mg dose, similar reductions in glomerular filtration rate were observed.⁴ At the present time, it is unclear whether sirolimus exerts a direct nephrotoxic effect or merely potentiates the nephrotoxicity of cyclosporine. Another unexpected adverse effect observed in sirolimus-treated patients was the development of lymphoceles, which appeared to be

dose dependent.⁴

Other common adverse effects that have been reported include leukopenia, hypertension, anemia, nausea, vomiting, increases in liver enzymes, rash, and acne.^{4,19} Patients receiving sirolimus at the 5-mg dose exhibited a higher incidence of leukopenia, thrombocytopenia, hypokalemia, fever, arthralgias, diarrhea, and hyperlipidemia as compared with patients receiving the 2-mg dose, azathioprine, or placebo (Table 6).⁴

Patients receiving sirolimus also appear to be at greater risk for the development of herpes simplex infections, in particular at the 5-mg dose.^{4,29} However, the incidence of fungal, bacterial, or cytomegalovirus infection does not appear to increase with the use of this agent.^{4,28-30} Moreover, sirolimus-treated patients do not appear to be at increased risk for developing posttransplant proliferative disorders within the first six months of transplant.⁴

Drug interactions

Sirolimus is extensively metabolized by the cytochrome P450 3A4 isoenzyme, the same enzyme responsible for metabolism of cyclosporine and tacrolimus. Oral administration of cyclosporine with sirolimus significantly increases the AUC for sirolimus, as well as sirolimus blood trough concentrations.³³ A randomized crossover study was conducted in 20 stable renal allograft recipients who received sirolimus, cyclosporine, and prednisone for at least three months. For the purposes of this study, patients were randomized into two dosing regimens. In the first group ($n = 10$), patients took their sirolimus dose along with their morning cyclosporine for seven days; then they switched to a dosing regimen in which the sirolimus dose was taken four hours after the morning cyclosporine dose for seven days. In the second group ($n = 10$), patients took their sirolimus dose four hours

after the morning cyclosporine dose for the first seven days of the study. For days 8 through 14, cyclosporine and sirolimus were taken together. Pharmacokinetic profiles were performed on days 7, 14, and 15. Of the 20 patients evaluated, 18 had higher sirolimus AUC values during the period in which they took sirolimus and cyclosporine concomitantly (459 ± 207 ng/mL/hr versus 317 ± 149 ng/mL/hr). Similarly, sirolimus blood trough values also were noted to be higher (13.3 ± 7.1 ng/mL versus 8.9 ± 4.4 ng/mL). Other pharmacokinetic differences are outlined in Table 7.³⁴ The current recommendation is that sirolimus be administered four hours after the morning cyclosporine dose is administered to minimize the potential for toxicity.

Pharmacokinetic studies with tacrolimus have not been performed to date, as all of the clinical trials thus far have utilized cyclosporine as the primary immunosuppressive agent. If protocols are implemented to study the clinical efficacy of tacrolimus used in combination with sirolimus, pharmacokinetic data will be essential for appropriate dosing of these agents.

As sirolimus is extensively metabolized by cytochrome P450, agents that are metabolized via cytochrome P450 or act as substrates for this isoenzyme or *p*-glycoprotein should be used with caution because of the potential to affect sirolimus blood levels. Drug interaction studies have been conducted with several agents including acyclovir, digoxin, glibenclamide, nifedipine, norgestrel and ethinyl estradiol, prednisolone, and trimethoprim-sulfamethoxazole. No clinically significant interactions have been observed with use of these agents and sirolimus. Noted below are specific drug-drug interactions that have been documented.

Diltiazem. Oral administration of diltiazem to 18 healthy volunteers receiving sirolimus led to a significant increase in sirolimus AUC, C_{max} , and

Table 7.

Pharmacokinetic Values for Sirolimus with and without Concomitant Administration of Cyclosporine^{a,b}

Sirolimus Pharmacokinetic Parameter	Concomitant Sirolimus and Cyclosporine Administration	Sirolimus Administration 4 hr after Cyclosporine	n	p
AUC (ng·mL ⁻¹ ·hr ⁻¹)	459 ± 207	317 ± 149	20	0.001
C _{min} (ng/mL)	13.3 ± 7.1	8.9 ± 4.4	20	<0.001
C _{max} (ng/mL)	43.8 ± 20.6	25.5 ± 14.2	20	0.002
t _{max} (hr)	1.8 ± 0.9	2.5 ± 1.4	20	0.028

^aValues are expressed as mean ± standard deviation. AUC = total area under the curve, C_{min} = minimum blood concentration, C_{max} = peak blood concentration, t_{max} = time to peak concentration.

^bTable adapted from reference 33.

t_{max}. The pharmacokinetics of diltiazem were not altered by the concomitant administration of sirolimus. In patients who require use of diltiazem, sirolimus blood trough levels should be monitored with appropriate adjustments in dose as necessary.⁴

Ketoconazole. Administration of ketoconazole has been reported to cause a 10.9-fold increase in sirolimus AUC, a fourfold increase in C_{max}, and a 38% increase in t_{max}. The terminal half-life of sirolimus is unchanged. Sirolimus does not appear to alter the pharmacokinetics of ketoconazole. It is recommended that ketoconazole not be administered to patients receiving sirolimus.⁴

Rifampin. Administration of rifampin has been reported to increase oral clearance of sirolimus fivefold, which is consistent with a mean decrease in AUC of 82% and a 71% decrease in C_{max}. Alternative agents should be used when feasible.⁴

Corticosteroids, ganciclovir, nifedipine, gemfibrozil, and the HMG-CoA-reductase inhibitors have been used in clinical trials with sirolimus without an increase in adverse reactions.^{4,18} Although the HMG-CoA-reductase inhibitors appeared to be well tolerated when used in conjunction with sirolimus and cyclosporine in the Phase III trials, all patients should be monitored closely because of the risk of rhabdomyolysis. To date, no clinical experience with the concomitant use of sirolimus with other immunosuppressives, such as

muromonab-CD3 and antilymphocyte globulins, has been reported.

Dosage and administration

Sirolimus should be administered concomitantly with cyclosporine and corticosteroids to prevent acute renal allograft rejection. Because of the pharmacokinetic interaction between cyclosporine and sirolimus, the daily dose of sirolimus should be given four hours after cyclosporine is administered to minimize the potential for adverse effects. Dosing of sirolimus with respect to food intake should be consistent to minimize intrapatient variability in oral absorption. Sirolimus oral solution should be thoroughly mixed with orange juice or water and consumed immediately. Apple juice, grapefruit juice, or other liquids should not be used. Only glass containers should be used to administer sirolimus.

In Phase III clinical trials, loading doses of 6 and 15 mg were given initially within 24 to 48 hours after transplantation, followed by a 2- or 5-mg/day dose, respectively. While both doses were associated with favorable outcomes, patients receiving the 5-mg dose experienced more drug-related adverse events without improved efficacy.⁴ Hence, the labeled recommendation is that de novo transplant patients receive a 6-mg loading dose as soon as possible after transplantation. The recommended maintenance dose of sirolimus is 2 mg per day. Use of higher

doses of sirolimus (such as the 5-mg dose) may be warranted in African-American patients who exhibit a reduced rate and extent of absorption and higher failure rates with the 2-mg dose.

Dosage adjustments are not necessary for renal impairment or age. In patients with hepatic impairment, the maintenance dose of sirolimus should be reduced by one third. It is not necessary to reduce the loading dose. The safety and efficacy of sirolimus in children less than 13 years of age have not been established. In children 13 years of age or older who weigh less than 40 kg, the initial dose should be adjusted based on body surface area. The recommended loading dose is 3 mg/m² with a recommended maintenance dose of 1 mg/m²/day.⁴

Sirolimus is contraindicated in patients with hypersensitivity to sirolimus and in those with known hypersensitivity to macrolide antibiotics. Sirolimus has been designated to pregnancy category C; therefore, the risks versus benefit to the patient and the fetus must be strongly considered.⁴ Contraception should be used by all women of childbearing potential during and for three months after discontinuation of sirolimus therapy. Similarly, it is not known whether sirolimus is excreted in human breast milk. As many agents are excreted in human milk, sirolimus should not be administered to a patient who is breast-feeding.

Dosage forms

Sirolimus is available as an oral solution in a concentration of 1 mg/mL.⁴ Sirolimus oral solution will be available in a 2- or 5-oz amber bottle or unit dose laminated aluminum pouches. The unit dose pouches will be available in three sizes: 1 mL (1 mg/mL), 2 mL (1 mg/mL), and 5 mL (1 mg/mL). Both the oral solution bottles and pouches should be stored protected from light and refrigerated at 2 to 8 °C. Sirolimus oral solution is stable for 12 months if the container is not opened and is kept refrigerated. Once the bottle is opened, the contents should be used within 30 days. The solution (both the bottle and pouches) may be stored at room temperature up to 25 °C for several days if necessary, but no longer than 30 days. The solution remains stable in the oral syringe provided for 24 hours at room temperature. A supply of disposable amber syringes and caps is provided for daily use. The syringe should be discarded after a single use.

The bottled sirolimus solution may develop a slight haze when refrigerated.⁴ If this should occur, the product should be left at room temperature and gently shaken until the haze disappears. The presence of haze does not affect the composition of the product.

A capsule formulation is expected to be approved in the near future.

Economic issues

The introduction of sirolimus will provide clinicians with another therapeutic alternative for treating transplant recipients and may enable them to treat patients on the basis of specific demographic and immunologic risk factors. Mycophenolate mofetil was introduced into clinical practice about three years ago and rapidly replaced azathioprine as the second adjunctive agent (in addition to corticosteroids) in many transplant centers. No direct comparative studies between mycophenolate mofetil and sirolimus have been performed. Comparative clinical trials with SDZ-RAD, a derivative of sirolimus, and mycophenolate mofetil have just been initiated. Results of this head-to-head comparison may better enable clinicians to establish the most efficacious triple-drug regimen. Notwithstanding, the clinical toxicities of each agent must be considered, in conjunction with patient-specific risk factors, when deciding which agent to ultimately employ.

Currently, the estimated drug cost for maintenance therapy with sirolimus is \$3946 per year, which is less than the cost associated with mycophenolate mofetil, which is about \$6500 per year.³⁴ Because specific immunosuppressive regimens vary from center to center, the average wholesale prices for the maintenance immunosuppressive agents em-

ployed after transplantation are compared in Table 8 so that clinicians can compare the drug costs of their specific immunosuppressive protocol with a sirolimus-based regimen. The overall increase in drug costs associated with some of the newer immunosuppressive agents may be offset by reductions in corticosteroid use and in the costs associated with managing corticosteroid-related toxicities, lower dosage requirements for cyclosporine, reduced incidence and severity of acute and chronic rejection, and reduced need for antibody therapy (muromonab-CD3, antithymocyte globulin) both for induction and rejection therapy. However, well-designed comparative pharmaco-economic analyses are required for both mycophenolate and sirolimus to assess their overall impact on health care costs, taking into consideration costs associated with managing drug-specific toxicities, as well as health outcomes data.

Similar agents under consideration

SDZ-RAD (Novartis Pharmaceuticals) was developed to overcome the unfavorable pharmacokinetic characteristics of sirolimus, namely the relatively poor oral bioavailability. SDZ-RAD was obtained by fermenting the actinomycete strain A91-259211 and subsequent *O-*

Table 8.

Comparison of Average Wholesale Prices for Usual Doses of Maintenance Immunosuppressive Agents^a

Immunosuppressive Agent	Usual Induction Doses in De Novo Patients	Estimated Drug Cost per Day in De Novo Patients ^{b,c}	Usual Maintenance Doses in Stable Patients	Estimated Maintenance Immunosuppressive Costs per Year ^{b,c}
Cyclosporine ^d	10 mg/kg/day	\$41.50	4 mg/kg/day	\$ 5878.00
Tacrolimus	0.2 mg/kg/day	\$39.25	0.1 mg/kg/day	\$ 7056.00
Mycophenolate	2 g/day	\$18.00	2 g/day	\$ 6479.00
Azathioprine	2 mg/kg/day	\$ 4.37	2 mg/kg/day	\$ 1573.00
Prednisone	1 mg/kg/day	\$ 0.50	0.2 mg/kg/day	\$ 44.00
Sirolimus	2 mg/day	\$10.96	2 mg/day	\$3946.00

^aReference 34.

^bDrug costs for a 70-kg person.

^cActual costs will vary from center to center, depending on specific doses and protocols employed at each institution.

^dNeoral by Novartis.

alkylation of sirolimus at position 40.³⁵ The introduction of a 2-hydroxyethyl group in position 40 led to the development of SDZ-RAD, which exhibits comparable in vitro immunosuppressive activity to that of sirolimus.³⁵ Rat studies suggest that SDZ-RAD is better absorbed than sirolimus. Oral absorption of SDZ-RAD was reported to be 40% compared with 14% for sirolimus, with an absolute bioavailability of 11% for SDZ-RAD and 6% for sirolimus.³⁶ The clinical toxicities of SDZ-RAD are similar to those noted for sirolimus.³⁷ SDZ-RAD is currently in Phase III trials to evaluate its efficacy in preventing acute rejection among renal allograft recipients.

Recommendations and critical issues

Sirolimus is a potent novel immunosuppressive agent with proven efficacy in the prevention of acute rejection after renal transplantation. The introduction of sirolimus will give clinicians a new therapeutic alternative for managing transplant recipients. Now that several alternatives for immunosuppression are available, it is important for clinicians to start considering patient-specific demographic and immunologic characteristics when devising immunosuppressive regimens to better optimize graft outcomes while minimizing immunosuppressant-related toxicities. Use of sirolimus may lead to effective therapeutic strategies for sparing the use of cyclosporine and corticosteroids. Clinical and economic analyses are required to determine the cost savings that are associated with the use of sirolimus resulting from its potential for reducing the use of cyclosporine or steroids and, perhaps, its potential to improve graft survival secondary to a reduced incidence of acute rejection. Well-controlled studies are needed to further clarify the role of sirolimus in treating refractory rejection and its impact on chronic rejec-

tion. Renal function should be monitored closely in all patients, with dosage titration of immunosuppressants, as appropriate, to minimize the development of nephrotoxicity. Aggressive management of the lipid disorders associated with the administration of sirolimus will be essential to minimize cardiovascular morbidity.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Rapamune safely and effectively. See full prescribing information for Rapamune.

RAPAMUNE (sirolimus) ORAL SOLUTION AND TABLETS

Initial U.S. Approval: 1999

WARNING: IMMUNOSUPPRESSION, USE IS NOT RECOMMENDED IN LIVER OR LUNG TRANSPLANT PATIENTS

See Full Prescribing Information for complete Boxed Warning.

- Increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression (5.1). Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune.
- The safety and efficacy of Rapamune as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended (5.2, 5.3).
 - Liver Transplantation – Excess mortality, graft loss, and hepatic artery thrombosis (5.2).
 - Lung Transplantation – Bronchial anastomotic dehiscence (5.3).

RECENT MAJOR CHANGES

Dosage and Administration

- Therapeutic Drug Monitoring (2.3) 10/2009

Warnings and Precautions

- Liver Transplantation (5.2) 09/2009
- Latent Viral infections (5.10) 10/2009

INDICATIONS AND USAGE

Rapamune is an immunosuppressive agent indicated for the prophylaxis of organ rejection in patients aged ≥13 years receiving renal transplants.

- Patients at low- to moderate-immunologic risk: Use initially with cyclosporine (CsA) and corticosteroids. CsA withdrawal is recommended 2-4 months after transplantation (1.1).
- Patients at high-immunologic risk: Use in combination with cyclosporine and corticosteroids for the first 12 months following transplantation (1.1). Safety and efficacy of CsA withdrawal has not been established in high risk patients (1.1, 1.2, 14.3).
- Therapeutic drug monitoring is recommended for all patients (2.3, 5.14).

DOSAGE AND ADMINISTRATION

- Take once daily by mouth, consistently with or without food. Take the initial dose as soon as possible after transplantation and 4 hours after CsA (2, 7.1). Adjust the Rapamune maintenance dose to achieve sirolimus trough concentrations within the target-range (2.3).

PATIENTS AT LOW- TO MODERATE-IMMUNOLOGIC RISK

- Rapamune and Cyclosporine Combination Therapy: One loading dose of 6 mg on day 1, followed by daily maintenance doses of 2 mg (2.1).
- Rapamune Following Cyclosporine Withdrawal: 2-4 months post-transplantation, withdraw CsA over 4-8 weeks (2.2).

PATIENTS AT HIGH-IMMUNOLOGIC RISK

- Rapamune and Cyclosporine Combination Therapy (for the first 12 months post-transplantation): One loading dose of up to 15 mg on day 1, followed by daily maintenance doses of 5 mg (2.2).

DOSAGE FORMS AND STRENGTHS

- Rapamune Oral Solution: 60 mg per 60 mL in amber glass bottle (3.1).
- Rapamune Tablets: 1 mg, white; 2 mg, yellow-to-beige (3.2).

CONTRAINDICATIONS

Hypersensitivity to Rapamune (4).

WARNINGS AND PRECAUTIONS

- Hypersensitivity Reactions (5.4)
- Angioedema (5.5)
- Fluid Accumulation and Wound Healing (5.6)
- Hyperlipidemia (5.7)
- Renal Function (5.8)
- Proteinuria (5.9)
- Latent Viral Infections (5.10)
- Interstitial Lung Disease (5.11)
- De Novo Use Without Cyclosporine (5.12)
- Increased Risk of Calcineurin Inhibitor-induced HUS/TTP/TMA (5.13)

ADVERSE REACTIONS

The most common (> 30%) adverse reactions are: peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Avoid concomitant use with strong CYP3A4/P-gp inducers or strong CYP3A4/P-gp inhibitors that decrease or increase sirolimus concentrations (7.4, 12.3).
- Exercise caution when administering with drugs that are inhibitors/inducers of CYP3A4/P-gp (7.4, 12.3).

USE IN SPECIFIC POPULATIONS

- Pregnancy: Use only if the potential benefit outweighs the potential risk to the embryo/fetus (8.1).
- Hepatic impairment: Reduce maintenance dose in patients with hepatic impairment (2.5, 8.6, 12.3).

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 11/2009

FULL PRESCRIBING INFORMATION: CONTENTS *

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FULL PRESCRIBING INFORMATION

BOX WARNING: IMMUNOSUPPRESSION, USE IS NOT RECOMMENDED IN LIVER OR LUNG TRANSPLANT PATIENTS

- Increased susceptibility to infection and the possible development of lymphoma and other malignancies may result from immunosuppression

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune®. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient [see *Warnings and Precautions* (5.1)].

- The safety and efficacy of Rapamune (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended [see *Warnings and Precautions* (5.2, 5.3)].
- Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT)

The use of Rapamune in combination with tacrolimus was associated with excess mortality and graft loss in a study in *de novo* liver transplant patients. Many of these patients had evidence of infection at or near the time of death.

In this and another study in *de novo* liver transplant patients, the use of Rapamune in combination with cyclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death [see *Warnings and Precautions* (5.2)].

- Lung Transplantation – Bronchial Anastomotic Dehiscence

Cases of bronchial anastomotic dehiscence, most fatal, have been reported in *de novo* lung transplant patients when Rapamune has been used as part of an immunosuppressive regimen [see *Warnings and Precautions* (5.3)].

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Organ Rejection in Renal Transplantation

Rapamune (sirolimus) is indicated for the prophylaxis of organ rejection in patients aged 13 years or older receiving renal transplants. Therapeutic drug monitoring is recommended for all

patients receiving Rapamune [see *Dosage and Administration* (2.3), *Warnings and Precautions* (5.15)].

In patients at low- to moderate-immunologic risk, it is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids; cyclosporine should be withdrawn 2 to 4 months after transplantation [see *Dosage and Administration* (2.1)].

In patients at high-immunologic risk (defined as Black recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reason and/or patients with high panel-reactive antibodies [PRA; peak PRA level > 80%]), it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first year following transplantation [see *Dosage and Administration* (2.2), *Clinical Studies* (14.2)].

1.2 Limitations of Use

Cyclosporine withdrawal has not been studied in patients with Banff Grade 3 acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, those with serum creatinine > 4.5 mg/dL, Black patients, patients of multi-organ transplants, secondary transplants, or those with high levels of panel-reactive antibodies [see *Clinical Studies* (14.2)].

In patients at high-immunologic risk, the safety and efficacy of Rapamune used in combination with cyclosporine and corticosteroids has not been studied beyond one year; therefore after the first 12 months following transplantation, any adjustments to the immunosuppressive regimen should be considered on the basis of the clinical status of the patient [see *Clinical Studies* (14.3)].

In pediatric patients, the safety and efficacy of Rapamune have not been established in patients < 13 years old, or in pediatric (< 18 years) renal transplant patients considered at high-immunologic risk [see *Adverse Reactions* (6.5), *Clinical Studies* (14.6)]. The safety and efficacy of *de novo* use of Rapamune without cyclosporine have not been established in renal transplant patients [see *Warnings and Precautions* (5.12)].

The safety and efficacy of **conversion from calcineurin inhibitors to Rapamune** in maintenance renal transplant patients have not been established [see *Clinical Studies* (14.2)].

2 DOSAGE AND ADMINISTRATION

Rapamune is to be administered orally once daily, consistently with or without food [see *Dosage and Administration* (2.4), *Clinical Pharmacology* (12.3)].

Tablets should not be crushed, chewed or split. Patients unable to take the tablets should be prescribed the solution and instructed in its use.

The initial dose of Rapamune should be administered as soon as possible after transplantation. It is recommended that Rapamune be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED) [see *Drug Interactions* (7.2)].

Frequent Rapamune dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once Rapamune maintenance dose is adjusted, patients should continue on the new maintenance dose for at least 7 to 14 days before further dosage adjustment with concentration monitoring. In most patients, dose adjustments can be based on simple proportion: new Rapamune dose = current dose x (target concentration/current concentration). A loading dose should be considered in addition to a new maintenance dose when it is necessary to increase sirolimus trough concentrations: Rapamune loading dose = 3 x (new maintenance dose - current maintenance dose). The maximum Rapamune dose administered on any day should not exceed 40 mg. If an estimated daily dose exceeds 40 mg due to the addition of a loading dose, the loading dose should be administered over 2 days. Sirolimus trough concentrations should be monitored at least 3 to 4 days after a loading dose(s).

Two milligrams (2 mg) of Rapamune Oral Solution have been demonstrated to be clinically equivalent to 2 mg Rapamune Tablets; hence, are interchangeable on a mg-to-mg basis. However, it is not known if higher doses of Rapamune Oral Solution are clinically equivalent to higher doses of Rapamune Tablets on a mg-to-mg basis [see *Clinical Pharmacology (12.3)*].

2.1 Patients at Low- to Moderate-Immunologic Risk

Rapamune and Cyclosporine Combination Therapy

For *de novo* renal transplant patients, it is recommended that Rapamune Oral Solution and Tablets be used initially in a regimen with cyclosporine and corticosteroids. A loading dose of Rapamune equivalent to 3 times the maintenance dose should be given, i.e. a daily maintenance dose of 2 mg should be preceded with a loading dose of 6 mg. Therapeutic drug monitoring should be used to maintain sirolimus drug concentrations within the target-range [see *Dosage and Administration (2.3)*].

Rapamune Following Cyclosporine Withdrawal

At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks, and the Rapamune dose should be adjusted to obtain sirolimus whole blood trough concentrations within the target-range [see *Dosage and Administration (2.3)*]. Because cyclosporine inhibits the metabolism and transport of sirolimus, sirolimus concentrations may decrease when cyclosporine is discontinued, unless the Rapamune dose is increased [see *Clinical Pharmacology (12.3)*].

2.2 Patients at High-Immunologic Risk

In patients with high-immunologic risk, it is recommended that Rapamune be used in combination with cyclosporine and corticosteroids for the first 12 months following transplantation [see *Clinical Studies (14.2)*]. The safety and efficacy of this combination in high-immunologic risk patients has not been studied beyond the first 12 months. Therefore, after the first 12 months following transplantation, any adjustments to the immunosuppressive regimen should be considered on the basis of the clinical status of the patient.

For patients receiving Rapamune with cyclosporine, Rapamune therapy should be initiated with a loading dose of up to 15 mg on day 1 post-transplantation. Beginning on day 2, an initial maintenance dose of 5 mg/day should be given. A trough level should be obtained between days 5 and 7, and the daily dose of Rapamune should thereafter be adjusted [see *Dosage and Administration* (2.3)].

The starting dose of cyclosporine should be up to 7 mg/kg/day in divided doses and the dose should subsequently be adjusted to achieve target whole blood trough concentrations [see *Dosage and Administration* (2.3)]. Prednisone should be administered at a minimum of 5 mg/day.

Antibody induction therapy may be used.

2.3 Therapeutic Drug Monitoring

Monitoring of sirolimus trough concentrations is recommended for all patients, especially in those patients likely to have altered drug metabolism, in patients \geq 13 years who weigh less than 40 kg, in patients with hepatic impairment, when a change in the Rapamune dosage form is made, and during concurrent administration of strong CYP3A4 inducers and inhibitors [see *Drug Interactions* (7)].

Therapeutic drug monitoring should not be the sole basis for adjusting Rapamune therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy findings, and laboratory parameters.

When used in combination with cyclosporine, sirolimus trough concentrations should be maintained within the target-range [see *Clinical Studies* (14), *Clinical Pharmacology* (12.3)]. Following cyclosporine withdrawal in transplant patients at low- to moderate-immunologic risk, the target sirolimus trough concentrations should be 16 to 24 ng/mL for the first year following transplantation. Thereafter, the target sirolimus concentrations should be 12 to 20 ng/mL.

The above recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. Because the measured sirolimus whole blood concentrations depend on the type of assay used, the concentrations obtained by these different methodologies are not interchangeable [see *Warnings and Precautions* (5.14), *Clinical Pharmacology* (12.3)]. Adjustments to the targeted range should be made according to the assay utilized to determine sirolimus trough concentrations. Since results are assay and laboratory dependent, and the results may change over time, adjustments to the targeted therapeutic range must be made with a detailed knowledge of the site-specific assay used. A discussion of different assay methods is contained in Clinical Therapeutics, Volume 22, Supplement B, April 2000 [see *References* (15)].

2.4 Patients with Low Body Weight

The initial dosage in patients \geq 13 years who weigh less than 40 kg should be adjusted, based on body surface area, to 1 mg/m²/day. The loading dose should be 3 mg/m².

2.5 Patients with Hepatic Impairment

It is recommended that the maintenance dose of Rapamune be reduced by approximately one third in patients with mild or moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment. It is not necessary to modify the Rapamune loading dose [see *Clinical Pharmacology (12.3)*].

2.6 Patients with Renal Impairment

Dosage adjustment is not needed in patients with impaired renal function [see *Use in Specific Populations (8.7)*].

2.7 Instructions for Dilution and Administration of Rapamune Oral Solution

The amber oral dose syringe should be used to withdraw the prescribed amount of Rapamune Oral Solution from the bottle. Empty the correct amount of Rapamune from the syringe into only a glass or plastic container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. No other liquids, including grapefruit juice, should be used for dilution [see *Drug Interactions (7.3)*, *Clinical Pharmacology (12.3)*]. Stir vigorously and drink at once. Refill the container with an additional volume [minimum of four (4) ounces (1/2 cup, 120 mL)] of water or orange juice, stir vigorously, and drink at once.

Rapamune Oral Solution contains polysorbate 80, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC). This should be considered during the preparation and administration of Rapamune Oral Solution. It is important that these recommendations be followed closely.

3 DOSAGE FORMS AND STRENGTHS

3.1 Rapamune Oral Solution

- 60 mg per 60 mL in amber glass bottle.

3.2 Rapamune Tablets

- 1 mg, white, triangular-shaped tablets marked “RAPAMUNE 1 mg” on one side.
- 2 mg, yellow-to-beige triangular-shaped tablets marked “RAPAMUNE 2 mg” on one side.

4 CONTRAINDICATIONS

Rapamune is contraindicated in patients with a hypersensitivity to Rapamune [see *Warnings and Precautions (5.4)*].

5 WARNINGS AND PRECAUTIONS

5.1 Increased Susceptibility to Infection and the Possible Development of Lymphoma

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression. The rates of lymphoma/lymphoproliferative disease observed in Studies 1 and 2 were 0.7-3.2% (for Rapamune-treated patients) versus 0.6-0.8% (azathioprine and placebo control) [see *Adverse Reactions (6.1)* and *(6.2)*]. Oversuppression of the immune system can also increase susceptibility to infection, including opportunistic infections such as tuberculosis, fatal infections, and sepsis. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use Rapamune. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

5.2 Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT)

The safety and efficacy of Rapamune as immunosuppressive therapy have not been established in liver transplant patients; therefore, such use is not recommended. The use of Rapamune has been associated with adverse outcomes in patients following liver transplantation, including excess mortality, graft loss and Hepatic Artery Thrombosis (HAT).

In a study in *de novo* liver transplant patients, the use of Rapamune in combination with tacrolimus was associated with excess mortality and graft loss (22% in combination versus 9% on tacrolimus alone). Many of these patients had evidence of infection at or near the time of death.

In this and another study in *de novo* liver transplant patients, the use of Rapamune in combination with cyclosporine or tacrolimus was associated with an increase in HAT (7% in combination versus 2% in the control arm); most cases of HAT occurred within 30 days post-transplantation, and most led to graft loss or death.

In a clinical study in stable liver transplant patients 6-144 months post-liver transplantation and receiving a CNI-based regimen, an increased number of deaths was observed in the group converted to a Rapamune-based regimen compared to the group who was continued on a CNI-based regimen, although the difference was not statistically significant (3.8% versus 1.4%) [see *Clinical Studies (14.5)*].

5.3 Lung Transplantation – Bronchial Anastomotic Dehiscence

Cases of bronchial anastomotic dehiscence, most fatal, have been reported in *de novo* lung transplant patients when Rapamune has been used as part of an immunosuppressive regimen.

The safety and efficacy of Rapamune as immunosuppressive therapy have not been established in lung transplant patients; therefore, such use is not recommended.

5.4 Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, exfoliative dermatitis and hypersensitivity vasculitis, have been associated with the administration of Rapamune [see *Adverse Reactions* (6.6)].

5.5 Angioedema

Rapamune has been associated with the development of angioedema. The concomitant use of Rapamune with other drugs known to cause angioedema, such as ACE-inhibitors, may increase the risk of developing angioedema.

5.6 Fluid Accumulation and Wound Healing

There have been reports of impaired or delayed wound healing in patients receiving Rapamune, including lymphocole and wound dehiscence [see *Adverse Reactions* (6.1)]. mTOR inhibitors such as sirolimus have been shown *in vitro* to inhibit production of certain growth factors that may affect angiogenesis, fibroblast proliferation, and vascular permeability. Lymphocole, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in patients treated with Rapamune [see *Adverse Reactions* (6.1)].

Appropriate measures should be considered to minimize such complications. Patients with a body mass index (BMI) greater than 30 kg/m² may be at increased risk of abnormal wound healing based on data from the medical literature.

There have also been reports of fluid accumulation, including peripheral edema, lymphedema, pleural effusion and pericardial effusions (including hemodynamically significant effusions and tamponade requiring intervention in children and adults), in patients receiving Rapamune.

5.7 Hyperlipidemia

Increased serum cholesterol and triglycerides requiring treatment occurred more frequently in patients treated with Rapamune compared with azathioprine or placebo controls in Studies 1 and 2 [see *Adverse Reactions* (6.1)]. There were increased incidences of hypercholesterolemia (43-46%) and/or hypertriglyceridemia (45-57%) in patients receiving Rapamune compared with placebo controls (each 23%). The risk/benefit should be carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Rapamune.

Any patient who is administered Rapamune should be monitored for hyperlipidemia. If detected, interventions such as diet, exercise, and lipid-lowering agents should be initiated as outlined by the National Cholesterol Education Program guidelines.

In clinical trials, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates appeared to be well-tolerated.

During Rapamune therapy with cyclosporine, patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects, as described in the respective labeling for these agents.

5.8 Renal Function

Renal function should be closely monitored during the co-administration of Rapamune with cyclosporine, because long-term administration of the combination has been associated with deterioration of renal function. Patients treated with cyclosporine and Rapamune were noted to have higher serum creatinine levels and lower glomerular filtration rates compared with patients treated with cyclosporine and placebo or azathioprine controls (Studies 1 and 2). The rate of decline in renal function in these studies was greater in patients receiving Rapamune and cyclosporine compared with control therapies.

Appropriate adjustment of the immunosuppressive regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. In patients at low- to moderate-immunologic risk, continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients. Caution should be exercised when using agents (e.g., aminoglycosides and amphotericin B) that are known to have a deleterious effect on renal function.

In patients with delayed graft function, Rapamune may delay recovery of renal function.

5.9 Proteinuria

Periodic quantitative monitoring of urinary protein excretion is recommended. In a study evaluating conversion from calcineurin inhibitors (CNI) to Rapamune in maintenance renal transplant patients 6-120 months post-transplant, increased urinary protein excretion was commonly observed from 6 through 24 months after conversion to Rapamune compared with CNI continuation [see *Clinical Studies (14.4), Adverse Reactions (6.4)*]. Patients with the greatest amount of urinary protein excretion prior to Rapamune conversion were those whose protein excretion increased the most after conversion. New onset nephrosis (nephrotic syndrome) was also reported as a treatment-emergent adverse event in 2.2% of the Rapamune conversion group patients in comparison to 0.4% in the CNI continuation group of patients. Nephrotic range proteinuria (defined as urinary protein to creatinine ratio > 3.5) was also reported in 9.2% in the Rapamune conversion group of patients in comparison to 3.7% in the CNI continuation group of patients. In some patients, reduction in the degree of urinary protein excretion was observed for individual patients following discontinuation of Rapamune. The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant patients have not been established.

5.10 Latent Viral Infections

Immunosuppressed patients are at increased risk for opportunistic infections, including activation of latent viral infections. These include BK virus-associated nephropathy, which has been observed in patients receiving immunosuppressants, including Rapamune. This infection may be associated with serious outcomes, including deteriorating renal function and renal graft loss [see *Adverse Reactions (6.6)*]. Patient monitoring may help detect patients at risk for BK virus-associated nephropathy. Reduction in immunosuppression should be considered for patients who develop evidence of BK virus-associated nephropathy.

5.11 Interstitial Lung Disease

Cases of interstitial lung disease (including pneumonitis, bronchiolitis obliterans organizing pneumonia [BOOP], and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the trough sirolimus concentration increases [see *Adverse Reactions* (6.6)].

5.12 *De Novo* Use Without Cyclosporine

The safety and efficacy of *de novo* use of Rapamune without cyclosporine is not established in renal transplant patients. In a multicenter clinical study, *de novo* renal transplant patients treated with Rapamune, mycophenolate mofetil (MMF), steroids, and an IL-2 receptor antagonist had significantly higher acute rejection rates and numerically higher death rates compared to patients treated with cyclosporine, MMF, steroids, and IL-2 receptor antagonist. A benefit, in terms of better renal function, was not apparent in the treatment arm with *de novo* use of Rapamune without cyclosporine. These findings were also observed in a similar treatment group of another clinical trial.

5.13 Increased Risk of Calcineurin Inhibitor-Induced Hemolytic Uremic Syndrome/Thrombotic Thrombocytopenic Purpura/Thrombotic Microangiopathy (HUS/TTP/TMA)

The concomitant use of Rapamune with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TTP/TMA) [see *Adverse Reactions* (6.6)].

5.14 Antimicrobial Prophylaxis

Cases of *Pneumocystis carinii* pneumonia have been reported in patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for 1 year following transplantation.

Cytomegalovirus (CMV) prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.

5.15 Assay for Sirolimus Therapeutic Drug Monitoring

The label-recommended 24-hour trough concentration ranges for sirolimus are based on chromatographic methods. Currently in clinical practice, sirolimus whole blood concentrations are being measured by both chromatographic and immunoassay methodologies. These concentration values are not interchangeable [see *Dosage and Administration* (2.3), *Clinical Pharmacology* (12.3)].

5.16 Skin Cancer Events

Patients on immunosuppressive therapy are at increased risk for skin cancer. Exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

5.17 Interaction with Strong Inhibitors and Inducers of CYP3A4 and/or P-gp

Co-administration of Rapamune with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended [see *Drug Interactions (7)*].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label.

- Increased susceptibility to infection, lymphoma, and malignancy [see *Boxed Warning, Warnings and Precautions (5.1)*]
- Excess mortality, graft loss, and hepatic artery thrombosis in liver transplant patients [see *Boxed Warning, Warnings and Precautions (5.2)*]
- Bronchial anastomotic dehiscence in lung transplant patients [see *Boxed Warning, Warnings and Precautions (5.3)*]
- Hypersensitivity reactions [see *Warnings and Precautions (5.4)*]
- Exfoliative dermatitis [see *Warnings and Precautions (5.4)*]
- Angioedema [see *Warnings and Precautions (5.5)*]
- Fluid Accumulation and Wound Healing [see *Warnings and Precautions (5.6)*]
- Hypertriglyceridemia, hypercholesterolemia [see *Warnings and Precautions (5.7)*]
- Decline in renal function in long-term combination of cyclosporine with Rapamune [see *Warnings and Precautions (5.8)*]
- Proteinuria [see *Warnings and Precautions (5.9)*]
- Interstitial lung disease [see *Warnings and Precautions (5.11)*]
- Increased risk of calcineurin inhibitor-induced hemolytic uremic syndrome/thrombotic thrombocytopenic purpura/thrombotic microangiopathy (HUS/TPP/TMA) [see *Warnings and Precautions (5.13)*].

The most common ($\geq 30\%$) adverse reactions observed with Rapamune in clinical studies are: peripheral edema, hypertriglyceridemia, hypertension, hypercholesterolemia, creatinine increased, constipation, abdominal pain, diarrhea, headache, fever, urinary tract infection, anemia, nausea, arthralgia, pain, and thrombocytopenia.

The following adverse reactions resulted in a rate of discontinuation of $> 5\%$ in clinical trials: creatinine increased, hypertriglyceridemia, and thrombotic thrombocytopenic purpura (TPP).

6.1 Clinical Studies Experience in Prophylaxis of Organ Rejection Following Renal Transplantation

The safety and efficacy of Rapamune Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials [see *Clinical Studies (14.1)*]. The safety profiles in the two studies were similar.

The incidence of adverse reactions in the randomized, double-blind, multicenter, placebo-controlled trial (Study 2) in which 219 renal transplant patients received Rapamune Oral Solution 2 mg/day, 208 received Rapamune Oral Solution 5 mg/day, and 124 received placebo is presented in the table below. The study population had a mean age of 46 years (range 15 to 71 years), the distribution was 67% male, and the composition by race was: White (78%), Black (11%), Asian (3%), Hispanic (2%), and Other (5%). All patients were treated with cyclosporine and corticosteroids. Data (\geq 12 months post-transplant) presented in the following table show the adverse reactions that occurred in at least one of the Rapamune treatment groups with an incidence of \geq 20%.

The safety profile of the tablet did not differ from that of the oral solution formulation [see *Clinical Studies (14.1)*].

In general, adverse reactions related to the administration of Rapamune were dependent on dose/concentration. Although a daily maintenance dose of 5 mg, with a loading dose of 15 mg, was shown to be safe and effective, no efficacy advantage over the 2 mg dose could be established for renal transplant patients. Patients receiving 2 mg of Rapamune Oral Solution per day demonstrated an overall better safety profile than did patients receiving 5 mg of Rapamune Oral Solution per day.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in one clinical trial of a drug cannot be directly compared with rates in the clinical trials of the same or another drug and may not reflect the rates observed in practice.

ADVERSE REACTIONS OCCURRING AT A FREQUENCY OF \geq 20% IN AT LEAST ONE OF THE RAPAMUNE TREATMENT GROUPS IN A STUDY OF PROPHYLAXIS OF ORGAN REJECTION FOLLOWING RENAL TRANSPLANTATION (%) AT \geq 12 MONTHS POST-TRANSPLANTATION (STUDY 2)^a

Adverse Reaction	Rapamune Oral Solution		
	2 mg/day (n = 218)	5 mg/day (n = 208)	Placebo (n = 124)
Peripheral edema	54	58	48
Hypertriglyceridemia	45	57	23
Hypertension	45	49	48
Hypercholesterolemia	43	46	23
Creatinine increased	39	40	38
Constipation	36	38	31
Abdominal pain	29	36	30

ADVERSE REACTIONS OCCURRING AT A FREQUENCY OF $\geq 20\%$ IN AT LEAST ONE OF THE RAPAMUNE TREATMENT GROUPS IN A STUDY OF PROPHYLAXIS OF ORGAN REJECTION FOLLOWING RENAL TRANSPLANTATION (%) AT ≥ 12 MONTHS POST-TRANSPLANTATION (STUDY 2)^a

Adverse Reaction	Rapamune Oral Solution		
	2 mg/day (n = 218)	5 mg/day (n = 208)	Placebo (n = 124)
Diarrhea	25	35	27
Headache	34	34	31
Fever	23	34	35
Urinary tract infection	26	33	26
Anemia	23	33	21
Nausea	25	31	29
Arthralgia	25	31	18
Thrombocytopenia	14	30	9
Pain	33	29	25
Acne	22	22	19
Rash	10	20	6
Edema	20	18	15

a: Patients received cyclosporine and corticosteroids.

The following adverse reactions were reported less frequently ($\geq 3\%$, but $< 20\%$)

- **Body as a Whole** – Sepsis, lymphocele, herpes zoster, herpes simplex.
- **Cardiovascular** – Venous thromboembolism (including pulmonary embolism, deep venous thrombosis), tachycardia.
- **Digestive System** – Stomatitis.
- **Hematologic and Lymphatic System** – Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS), leukopenia.
- **Metabolic/Nutritional** – Abnormal healing, increased lactic dehydrogenase (LDH), hypokalemia.
- **Musculoskeletal System** – Bone necrosis.
- **Respiratory System** – Pneumonia, epistaxis.
- **Skin** – Melanoma, squamous cell carcinoma, basal cell carcinoma.
- **Urogenital System** – Pyelonephritis, decline in renal function (creatinine increased) in long-term combination of cyclosporine with Rapamune [see *Warnings and Precautions* (5.8)].

Less frequently ($< 3\%$) occurring adverse reactions included: lymphoma/post-transplant lymphoproliferative disorder, mycobacterial infections (including *M. tuberculosis*), pancreatitis, cytomegalovirus (CMV), and Epstein-Barr virus.

Increased Serum Cholesterol and Triglycerides

The use of Rapamune in renal transplant patients was associated with increased serum cholesterol and triglycerides that may require treatment.

In Studies 1 and 2, in *de novo* renal transplant patients who began the study with fasting, total serum cholesterol < 200 mg/dL or fasting, total serum triglycerides < 200 mg/dL, there was an increased incidence of hypercholesterolemia (fasting serum cholesterol > 240 mg/dL) or hypertriglyceridemia (fasting serum triglycerides > 500 mg/dL), respectively, in patients receiving both Rapamune 2 mg and Rapamune 5 mg compared with azathioprine and placebo controls.

Treatment of new-onset hypercholesterolemia with lipid-lowering agents was required in 42-52% of patients enrolled in the Rapamune arms of Studies 1 and 2 compared with 16% of patients in the placebo arm and 22% of patients in the azathioprine arm.

Abnormal Healing

Abnormal healing events following transplant surgery include fascial dehiscence, incisional hernia, and anastomosis disruption (e.g., wound, vascular, airway, ureteral, biliary).

Malignancies

The table below summarizes the incidence of malignancies in the two controlled trials (Studies 1 and 2) for the prevention of acute rejection [see *Clinical Studies (14.1)*].

At 24 months (Study 1) and 36 months (Study 2), there were no significant differences among treatment groups.

INCIDENCE (%) OF MALIGNANCIES IN STUDY 1 (24 MONTHS) AND STUDY 2 (36 MONTHS) POST-TRANSPLANT^{a,b}

Malignancy	Rapamune	Rapamune	Azathioprine			
	Oral Solution	Oral Solution	2-3		mg/kg/day	
	2 mg/day	5 mg/day	Study 1	Study 2		
Study 1	Study 2	Study 1	Study 2	Study 1	Study 2	
	(n = 284)	(n = 227)	(n = 274)	(n = 219)	(n = 161)	(n = 130)
Lymphoma/ lymphoproliferative disease	0.7	1.8	1.1	3.2	0.6	0.8
Skin Carcinoma						
Any Squamous Cell ^c	0.4	2.7	2.2	0.9	3.8	3.0
Any Basal Cell ^c	0.7	2.2	1.5	1.8	2.5	5.3
Melanoma	0.0	0.4	0.0	1.4	0.0	0.0
Miscellaneous/Not Specified	0.0	0.0	0.0	0.0	0.0	0.8
Total	1.1	4.4	3.3	4.1	4.3	7.7
Other Malignancy	1.1	2.2	1.5	1.4	0.6	2.3

a: Patients received cyclosporine and corticosteroids.

b: Includes patients who prematurely discontinued treatment.

c: Patients may be counted in more than one category.

6.2 Rapamune Following Cyclosporine Withdrawal

The incidence of adverse reactions was determined through 36 months in a randomized, multicenter, controlled trial (Study 3) in which 215 renal transplant patients received Rapamune as a maintenance regimen following cyclosporine withdrawal, and 215 patients received Rapamune with cyclosporine therapy [see *Clinical Studies* (14.2)]. All patients were treated with corticosteroids. The safety profile prior to randomization (start of cyclosporine withdrawal) was similar to that of the 2 mg Rapamune groups in Studies 1 and 2.

Following randomization (at 3 months), patients who had cyclosporine eliminated from their therapy experienced higher incidences of the following adverse reactions: abnormal liver function tests (including increased AST/SGOT and increased ALT/SGPT), hypokalemia, thrombocytopenia, and abnormal healing. Conversely, the incidence of the following adverse events was higher in patients who remained on cyclosporine than those who had cyclosporine withdrawn from therapy: hypertension, cyclosporine toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperkalemia, hyperuricemia, and gum hyperplasia. Mean systolic and diastolic blood pressure improved significantly following cyclosporine withdrawal.

Malignancies

The incidence of malignancies in Study 3 [see *Clinical Studies (14.2)*] is presented in the table following.

In Study 3, the incidence of lymphoma/lymphoproliferative disease was similar in all treatment groups. The overall incidence of malignancy was higher in patients receiving Rapamune plus cyclosporine compared with patients who had cyclosporine withdrawn. Conclusions regarding these differences in the incidence of malignancy could not be made because Study 3 was not designed to consider malignancy risk factors or systematically screen subjects for malignancy. In addition, more patients in the Rapamune with cyclosporine group had a pretransplantation history of skin carcinoma.

INCIDENCE (%) OF MALIGNANCIES IN STUDY 3 (CYCLOSPORINE WITHDRAWAL STUDY) AT 36 MONTHS POST-TRANSPLANT^{a,b}

Malignancy	Nonrandomized (n = 95)	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Lymphoma/ lymphoproliferative disease	1.1	1.4	0.5
Skin Carcinoma			
Any Squamous Cell ^c	3.2	3.3	2.3
Any Basal Cell ^c	3.2	6.5	2.3
Melanoma	0.0	0.5	0.0
Miscellaneous/Not Specified	1.1	0.9	0.0
Total	4.2	7.9	3.7
Other Malignancy	3.2	3.3	1.9

a: Patients received cyclosporine and corticosteroids.

b: Includes patients who prematurely discontinued treatment.

c: Patients may be counted in more than one category.

6.3 High-Immunologic Risk Patients

Safety was assessed in 224 patients who received at least one dose of sirolimus with cyclosporine [see *Clinical Studies (14.3)*]. Overall, the incidence and nature of adverse events was similar to those seen in previous combination studies with Rapamune. The incidence of malignancy was 1.3% at 12 months.

6.4 Conversion from Calcineurin Inhibitors to Rapamune in Maintenance Renal Transplant Population

The safety and efficacy of conversion from calcineurin inhibitors to Rapamune in maintenance renal transplant population have not been established [see *Clinical Studies (14.4)*]. In an ongoing study evaluating the safety and efficacy of conversion from calcineurin inhibitors to Rapamune (initial target sirolimus concentrations of 12-20 ng/mL, and then 8-20 ng/mL, by chromatographic assay) in maintenance renal transplant patients, enrollment was stopped in the subset of patients (n = 87) with a baseline glomerular filtration rate of less than 40 mL/min. There was a higher rate of serious adverse events, including pneumonia, acute rejection, graft loss and death, in this stratum of the Rapamune treatment arm.

The subset of patients with a baseline glomerular filtration rate of less than 40 mL/min had 2 years of follow-up after randomization. In this population, the rate of pneumonia was 15/58 vs. 4/29, graft loss (excluding death with functioning graft loss) was 13/58 vs. 9/29, and death was 9/58 vs. 1/29 in the sirolimus conversion group and CNI continuation group, respectively.

In the subset of patients with a baseline glomerular filtration rate of greater than 40 mL/min, there was no benefit associated with conversion with regard to improvement in renal function and a greater incidence of proteinuria in the Rapamune conversion arm.

Overall in this study, a 5-fold increase in the reports of tuberculosis among sirolimus (11/551) and comparator (1/273) treatment groups was observed with 2:1 randomization scheme.

6.5 Pediatrics

Safety was assessed in a controlled clinical trial in pediatric (< 18 years of age) renal transplant patients considered at high-immunologic risk, defined as a history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy [see *Clinical Studies (14.6)*]. The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with a higher incidence of deterioration of renal function (creatinine increased) compared to calcineurin inhibitor-based therapy, serum lipid abnormalities (including, but not limited to, increased serum triglycerides and cholesterol), and urinary tract infections.

6.6 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Rapamune. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Body as a Whole** – Lymphedema.
- **Cardiovascular** – Pericardial effusion (including hemodynamically significant effusions and tamponade requiring intervention in children and adults).

- **Hematological/Lymphatic** – The concomitant use of Rapamune with a calcineurin inhibitor may increase the risk of calcineurin inhibitor-induced HUS/TTP/TMA [see *Warnings and Precautions (5.13)*]; pancytopenia, neutropenia.
- **Hepatobiliary Disorders** – Hepatotoxicity, including fatal hepatic necrosis, with elevated sirolimus trough concentrations.
- **Immune System** – Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis [see *Warnings and Precautions (5.4)*].
- **Infections** – Tuberculosis. BK virus associated nephropathy has been observed in patients receiving immunosuppressants, including Rapamune. This infection may be associated with serious outcomes, including deteriorating renal function and renal graft loss [see *Warnings and Precautions (5.10)*].
- **Metabolic/Nutritional** – Liver function test abnormal, AST/SGOT increased, ALT/SGPT increased, hypophosphatemia, hyperglycemia.
- **Respiratory** – Cases of interstitial lung disease (including pneumonitis, bronchiolitis obliterans organizing pneumonia [BOOP], and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the sirolimus trough concentration increases [see *Warnings and Precautions (5.11)*]; pulmonary hemorrhage; pleural effusion; alveolar proteinosis.
- **Skin** – Exfoliative dermatitis [see *Warnings and Precautions (5.4)*].
- **Urogenital** – Nephrotic syndrome, proteinuria, focal segmental glomerulosclerosis. Azoospermia has been reported with the use of Rapamune and has been reversible upon discontinuation of Rapamune in most cases.

7 DRUG INTERACTIONS

Sirolimus is known to be a substrate for both cytochrome P-450 3A4 (CYP3A4) and p-glycoprotein (P-gp). Inducers of CYP3A4 and P-gp may decrease sirolimus concentrations whereas inhibitors of CYP3A4 and P-gp may increase sirolimus concentrations.

7.1 Use with Cyclosporine

Cyclosporine, a substrate and inhibitor of CYP3A4 and P-gp, was demonstrated to increase sirolimus concentrations when co-administered with sirolimus. In order to diminish the effect of this interaction with cyclosporine, it is recommended that Rapamune be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED). If cyclosporine is withdrawn from combination therapy with Rapamune, higher doses of Rapamune are needed to maintain the recommended sirolimus trough concentration ranges [see *Dosage and Administration (2.1)*, *Clinical Pharmacology (12.3)*].

7.2 Strong Inducers and Strong Inhibitors of CYP3A4 and P-gp

Avoid concomitant use of sirolimus with strong inducers (e.g., rifampin, rifabutin) and strong inhibitors (e.g., ketoconazole, voriconazole, itraconazole, erythromycin, telithromycin, clarithromycin) of CYP3A4 and P-gp. Alternative agents with lesser interaction potential with sirolimus should be considered [see *Warnings and Precautions (5.17), Clinical Pharmacology (12.3)*].

7.3 Grapefruit Juice

Because grapefruit juice inhibits the CYP3A4-mediated metabolism of sirolimus, it must not be taken with or be used for dilution of Rapamune [see *Dosage and Administration (2.7), Drug Interactions (7.3), Clinical Pharmacology (12.3)*].

7.4 Inducers or Inhibitors of CYP3A4 and P-gp

Exercise caution when using sirolimus with drugs or agents that are modulators of CYP3A4 and P-gp. The dosage of Rapamune and/or the co-administered drug may need to be adjusted [see *Clinical Pharmacology (12.3)*].

- *Drugs that could increase sirolimus blood concentrations:*
Bromocriptine, cimetidine, cisapride, clotrimazole, danazol, diltiazem, fluconazole, HIV-protease inhibitors (e.g., ritonavir, indinavir), metoclopramide, nicardipine, troleandomycin, verapamil
- *Drugs and other agents that could decrease sirolimus concentrations:*
Carbamazepine, phenobarbital, phenytoin, rifapentine, St. John's Wort (*Hypericum perforatum*)
- *Drugs with concentrations that could increase when given with Rapamune:*
Verapamil

7.5 Vaccination

Immunosuppressants may affect response to vaccination. Therefore, during treatment with Rapamune, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to, the following: measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: Sirolimus was embryo/fetotoxic in rats when given in doses approximately 0.2 to 0.5 the human doses (adjusted for body surface area). Embryo/fetotoxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporine, rats had increased embryo/feto mortality compared with sirolimus alone. There were no effects on

rabbit development at a maternally toxic dosage approximately 0.3 to 0.8 times the human doses (adjusted for body surface area). There are no adequate and well-controlled studies in pregnant women. Effective contraception must be initiated before Rapamune therapy, during Rapamune therapy, and for 12 weeks after Rapamune therapy has been stopped. Rapamune should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

8.3 Nursing Mothers

Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Because many drugs are excreted in human milk, and because of the potential for adverse reactions in nursing infants from sirolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and efficacy of Rapamune in pediatric patients < 13 years have not been established.

The safety and efficacy of Rapamune Oral Solution and Rapamune Tablets have been established in children \geq 13 years judged to be at low- to moderate-immunologic risk. Use of Rapamune Oral Solution and Rapamune Tablets in this subpopulation of children \geq 13 years is supported by evidence from adequate and well-controlled trials of Rapamune Oral Solution in adults with additional pharmacokinetic data in pediatric renal transplantation patients [see *Clinical Pharmacology (12.3)*].

Safety and efficacy information from a controlled clinical trial in pediatric and adolescent (< 18 years of age) renal transplant patients judged to be at high-immunologic risk, defined as a history of one or more acute rejection episodes and/or the presence of chronic allograft nephropathy, do not support the chronic use of Rapamune Oral Solution or Tablets in combination with calcineurin inhibitors and corticosteroids, due to the higher incidence of lipid abnormalities and deterioration of renal function associated with these immunosuppressive regimens compared to calcineurin inhibitors, without increased benefit with respect to acute rejection, graft survival, or patient survival [see *Clinical Studies (14.5)*].

8.5 Geriatric Use

Clinical studies of Rapamune Oral Solution or Tablets did not include sufficient numbers of patients \geq 65 years to determine whether they respond differently from younger patients. Data pertaining to sirolimus trough concentrations suggest that dose adjustments based upon age in geriatric renal patients are not necessary. Differences in responses between the elderly and younger patients have not been identified. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, or cardiac function, and of concomitant disease or other drug therapy.

8.6 Patients with Hepatic Impairment

The maintenance dose of Rapamune should be reduced in patients with hepatic impairment [see *Dosage and Administration* (2.5), *Clinical Pharmacology* (12.3)].

8.7 Patients with Renal Impairment

Dosage adjustment is not required in patients with renal impairment [see *Dosage and Administration* (2.6), *Clinical Pharmacology* (12.3)].

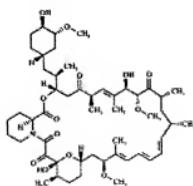
10 OVERDOSAGE

Reports of overdose with Rapamune have been received; however, experience has been limited. In general, the adverse effects of overdose are consistent with those listed in the adverse reactions section [see *Adverse Reactions* (6)].

General supportive measures should be followed in all cases of overdose. Based on the low aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent. In mice and rats, the acute oral LD₅₀ was greater than 800 mg/kg.

11 DESCRIPTION

Rapamune (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as rapamycin) is (3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R,27R,34aS)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-hexadecahydro-9,27-dihydroxy-3-[(1R)-2-[(1S,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3H-pyrido[2,1-c][1,4]oxaazacycloheptenatriacontine-1,5,11,28,29 (4H,6H,31H)-pentone. Its molecular formula is C₅₁H₇₉NO₁₃ and its molecular weight is 914.2. The structural formula of sirolimus is illustrated as follows.



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

Rapamune is available for administration as an oral solution containing 1 mg/mL sirolimus. Rapamune is also available as a white, triangular-shaped tablet containing 1 mg sirolimus, and as a yellow-to-beige triangular-shaped tablet containing 2 mg sirolimus.

The inactive ingredients in Rapamune Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5% - 2.5% ethanol.

The inactive ingredients in Rapamune Tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, *dl*-alpha tocopherol, and other ingredients. The 2 mg dosage strength also contains yellow iron oxide and brown iron oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sirolimus inhibits T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus:FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G₁ to the S phase of the cell cycle.

Studies in experimental models show that sirolimus prolongs allograft (kidney, heart, skin, islet, small bowel, pancreatico-duodenal, and bone marrow) survival in mice, rats, pigs, and/or primates. Sirolimus reverses acute rejection of heart and kidney allografts in rats and prolongs the graft survival in presensitized rats. In some studies, the immunosuppressive effect of sirolimus lasts up to 6 months after discontinuation of therapy. This tolerization effect is alloantigen-specific.

In rodent models of autoimmune disease, sirolimus suppresses immune-mediated events associated with systemic lupus erythematosus, collagen-induced arthritis, autoimmune type I diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host disease, and autoimmune uveoretinitis.

12.2 Pharmacodynamics

Orally-administered Rapamune, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of organ rejection in low- to moderate-immunologic risk renal transplant patients at 6 months following transplantation compared with either azathioprine or placebo [see *Clinical Studies (14.1)*]. There was no demonstrable efficacy advantage of a daily maintenance dose of 5 mg with a loading dose of 15 mg over a daily maintenance dose of 2 mg with a loading dose of 6 mg. Therapeutic drug monitoring should be used to maintain sirolimus drug levels within the target-range [see *Dosage and Administration (2.3)*].

12.3 Pharmacokinetics

Sirolimus pharmacokinetics activity have been determined following oral administration in healthy subjects, pediatric patients, hepatically impaired patients, and renal transplant patients.

The pharmacokinetic parameters of sirolimus in low- to moderate-immunologic risk adult renal transplant patients following multiple dosing with Rapamune 2 mg daily, in combination with cyclosporine and corticosteroids, is summarized in the following table.

MEAN \pm SD STEADY STATE SIROLIMUS PHARMACOKINETIC PARAMETERS IN LOW- TO MODERATE-IMMUNOLOGIC RISK ADULT RENAL TRANSPLANT PATIENTS FOLLOWING RAPAMUNE 2 MG DAILY^{a,b}

	Multiple Dose (daily dose)	
	Solution	Tablets
C _{max} (ng/mL)	14.4 \pm 5.3	15.0 \pm 4.9
t _{max} (hr)	2.1 \pm 0.8	3.5 \pm 2.4
AUC (ng·h/mL)	194 \pm 78	230 \pm 67
C _{min} (ng/mL) ^c	7.1 \pm 3.5	7.6 \pm 3.1
CL/F (mL/h/kg)	173 \pm 50	139 \pm 63

a: In presence of cyclosporine administered 4 hours before Rapamune dosing.

b: Based on data collected at months 1 and 3 post-transplantation.

c: Average C_{min} over 6 months.

Whole blood trough sirolimus concentrations, as measured by LC/MS/MS in renal transplant patients, were significantly correlated with AUC_{0-ss}. Upon repeated, twice-daily administration without an initial loading dose in a multiple-dose study, the average trough concentration of sirolimus increases approximately 2- to 3-fold over the initial 6 days of therapy, at which time steady-state is reached. A loading dose of 3 times the maintenance dose will provide near steady-state concentrations within 1 day in most patients [see *Dosage and Administration* (2.2.3), *Warning and Precautions* (5.14)].

Absorption

Following administration of Rapamune Oral Solution, the mean times to peak concentration (t_{max}) of sirolimus are approximately 1 hour and 2 hours in healthy subjects and renal transplant patients, respectively. The systemic availability of sirolimus is low, and was estimated to be approximately 14% after the administration of Rapamune Oral Solution. In healthy subjects, the mean bioavailability of sirolimus after administration of the tablet is approximately 27% higher relative to the solution. Sirolimus tablets are not bioequivalent to the solution; however, clinical equivalence has been demonstrated at the 2 mg dose level. Sirolimus concentrations, following the administration of Rapamune Oral Solution to stable renal transplant patients, are dose-proportional between 3 and 12 mg/m².

Food Effects

To minimize variability in sirolimus concentrations, both Rapamune Oral Solution and Tablets should be taken consistently with or without food [see *Dosage and Administration* (2)]. In healthy subjects, a high-fat meal (861.8 kcal, 54.9% kcal from fat) increased the mean total exposure (AUC) of sirolimus by 23 to 35%, compared with fasting. The effect of food on the mean sirolimus C_{max} was inconsistent depending on the Rapamune dosage form evaluated.

Distribution

The mean (\pm SD) blood-to-plasma ratio of sirolimus was 36 ± 18 in stable renal allograft patients, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (V_{ss/F}) of sirolimus is 12 ± 8 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins, mainly serum albumin (97%), α_1 -acid glycoprotein, and lipoproteins.

Metabolism

Sirolimus is a substrate for both CYP3A4 and P-gp. Sirolimus is extensively metabolized in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen. Inhibitors of CYP3A4 and P-gp increase sirolimus concentrations. Inducers of CYP3A4 and P-gp decrease sirolimus concentrations [see *Warnings and Precautions* (5.17) and *Drug Interactions* (7)]. Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven (7) major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.

Excretion

After a single dose of [¹⁴C] sirolimus oral solution in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine. The mean \pm SD terminal elimination half life ($t_{1/2}$) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.

Sirolimus Concentrations (Chromatographic Equivalent) Observed in Phase 3 Clinical Studies

The following sirolimus concentrations (chromatographic equivalent) were observed in phase 3 clinical studies [see *Clinical Studies* (14)].

SIROLIMUS WHOLE BLOOD TROUGH CONCENTRATIONS OBSERVED IN RENAL TRANSPLANT PATIENTS ENROLLED IN PHASE 3 STUDIES

Patient Population(Study number)	Treatment	Year 1		Year 3	
		Mean (ng/mL)	10 th – 90 th percentiles (ng/mL)	Mean (ng/mL)	10 th – 90 th percentiles (ng/mL)
Low-to-moderate risk (Studies 1 & 2)	Rapamune (2 mg/day) + CsA	7.2	3.6 – 11	–	–
	Rapamune (5 mg/day) + CsA	14	8 – 22	–	–
Low-to-moderate risk (Study 3)	Rapamune + CsA	8.6	5 – 13 ^a	9.1	5.4 – 14
	Rapamune alone	19	14 – 22 ^a	16	11 – 22
High risk (Study 4)	Rapamune + CsA	15.7	5.4 – 27.3 ^b	–	–
		11.8	6.2 – 16.9 ^c		
		11.5	6.3 – 17.3 ^d		

a: Months 4 through 12

b: Up to Week 2; observed CsA C_{min} was 217 (56 – 432) ng/mL

c: Week 2 to Week 26; observed CsA C_{min} range was 174 (71 – 288) ng/mL

d: Week 26 to Week 52; observed CsA C_{min} was 136 (54.5 – 218) ng/mL

The withdrawal of cyclosporine and concurrent increases in sirolimus trough concentrations to steady-state required approximately 6 weeks. Following cyclosporine withdrawal, larger Rapamune doses were required due to the absence of the inhibition of sirolimus metabolism and transport by cyclosporine and to achieve higher target sirolimus trough concentrations during concentration-controlled administration [see *Dosage and Administration (2.1), Drug Interactions (7.1)*].

Pharmacokinetics in Specific Populations

Hepatic Impairment

Rapamune was administered as a single, oral dose to subjects with normal hepatic function and to patients with Child-Pugh classification A (mild), B (moderate), or C (severe) hepatic impairment. Compared with the values in the normal hepatic function group, the patients with mild, moderate, and severe hepatic impairment had 43%, 94%, and 189% higher mean values for sirolimus AUC, respectively, with no statistically significant differences in mean C_{max}. As the severity of hepatic impairment increased, there were steady increases in mean sirolimus t_{1/2}, and decreases in the mean sirolimus clearance normalized for body weight (CL/F/kg).

The maintenance dose of Rapamune should be reduced by approximately one third in patients with mild-to-moderate hepatic impairment and by approximately one half in patients with severe hepatic impairment [see *Dosage and Administration (2.5)*]. It is not necessary to modify

the Rapamune loading dose in patients with mild, moderate, and severe hepatic impairment. Therapeutic drug monitoring is necessary in all patients with hepatic impairment [see *Dosage and Administration* (2.3)].

Renal Impairment

The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites in healthy volunteers. The loading and the maintenance doses of Rapamune need not be adjusted in patients with renal impairment [see *Dosage and Administration* (2.6)].

Pediatric

Sirolimus pharmacokinetic data were collected in concentration-controlled trials of pediatric renal transplant patients who were also receiving cyclosporine and corticosteroids. The target ranges for trough concentrations were either 10-20 ng/mL for the 21 children receiving tablets, or 5-15 ng/mL for the one child receiving oral solution. The children aged 6-11 years (n = 8) received mean \pm SD doses of 1.75 ± 0.71 mg/day (0.064 ± 0.018 mg/kg, 1.65 ± 0.43 mg/m 2). The children aged 12-18 years (n = 14) received mean \pm SD doses of 2.79 ± 1.25 mg/day (0.053 ± 0.0150 mg/kg, 1.86 ± 0.61 mg/m 2). At the time of sirolimus blood sampling for pharmacokinetic evaluation, the majority (80%) of these pediatric patients received the Rapamune dose at 16 hours after the once-daily cyclosporine dose.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN \pm SD) IN PEDIATRIC RENAL TRANSPLANT PATIENTS (MULTIPLE-DOSE CONCENTRATION CONTROL)^{a,b}

Body		Age (y)	n	weight (kg)	C _{max,ss} (ng/mL)	t _{max,ss} (h)	C _{min,ss} (ng/mL)	AUC _{r,ss} (ng·h/mL)	CL/F ^c (mL/h/kg)	CL/F ^c (L/h/m 2)
6-11	12-18									
8	14	27 \pm 10	22.1 \pm 8.9		5.88 \pm 4.05	10.6 \pm 4.3	356 \pm 127	214 \pm 129	5.4 \pm 2.8	

a: Rapamune co-administered with cyclosporine oral solution [MODIFIED] (e.g., Neoral[®] Oral Solution) and/or cyclosporine capsules [MODIFIED] (e.g., Neoral[®] Soft Gelatin Capsules).

b: As measured by Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS)
c: Oral-dose clearance adjusted by either body weight (kg) or body surface area (m 2).

The table below summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically impaired renal function.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN \pm SD) IN PEDIATRIC PATIENTS WITH END-STAGE KIDNEY DISEASE MAINTAINED ON HEMODIALYSIS OR PERITONEAL DIALYSIS (1, 3, 9, 15 mg/m² SINGLE DOSE)*

Age Group (y)	n	t _{max} (h)	t _{1/2} (h)	CL/F/WT (mL/h/kg)
5-11	9	1.1 \pm 0.5	71 \pm 40	580 \pm 450
12-18	11	0.79 \pm 0.17	55 \pm 18	450 \pm 232

* All subjects received Rapamune Oral Solution.

Geriatric

Clinical studies of Rapamune did not include a sufficient number of patients > 65 years of age to determine whether they will respond differently than younger patients. After the administration of Rapamune Oral Solution or Tablets, sirolimus trough concentration data in renal transplant patients > 65 years of age were similar to those in the adult population 18 to 65 years of age.

Gender

Sirolimus clearance in males was 12% lower than that in females; male subjects had a significantly longer t_{1/2} than did female subjects (72.3 hours versus 61.3 hours). Dose adjustments based on gender are not recommended.

Race

In the phase 3 trials using Rapamune solution or tablets and cyclosporine oral solution [MODIFIED] (e.g., Neoral[®] Oral Solution) and/or cyclosporine capsules [MODIFIED] (e.g., Neoral[®] Soft Gelatin Capsules) [see *Clinical Studies (14)*], there were no significant differences in mean trough sirolimus concentrations over time between Black (n = 190) and non-Black (n = 852) patients during the first 6 months after transplantation.

Drug-Drug Interactions

Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-gp. The pharmacokinetic interaction between sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

Cyclosporine: Cyclosporine is a substrate and inhibitor of CYP3A4 and P-gp. Sirolimus should be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED). Sirolimus concentrations may decrease when cyclosporine is discontinued, unless the Rapamune dose is increased [see *Dosage and Administration (2.1)*, *Drug Interactions (7.1)*].

In a single-dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg Rapamune Tablets either simultaneously or 4 hours after a 300-mg dose of Neoral[®] Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, mean C_{max} and AUC were increased by 512% and 148%, respectively, relative to

administration of sirolimus alone. However, when given 4 hours after cyclosporine administration, sirolimus C_{max} and AUC were both increased by only 33% compared with administration of sirolimus alone.

In a single dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg Rapamune Oral Solution either simultaneously or 4 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, the mean C_{max} and AUC of sirolimus, following simultaneous administration were increased by 116% and 230%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus C_{max} and AUC were increased by only 37% and 80%, respectively, compared with administration of Rapamune alone.

In a single-dose cross-over drug-drug interaction study, 33 healthy volunteers received 5 mg Rapamune Oral Solution alone, 2 hours before, and 2 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). When given 2 hours before Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus C_{max} and AUC were comparable to those with administration of sirolimus alone. However, when given 2 hours after, the mean C_{max} and AUC of sirolimus were increased by 126% and 141%, respectively, relative to administration of sirolimus alone.

Mean cyclosporine C_{max} and AUC were not significantly affected when Rapamune Oral Solution was given simultaneously or when administered 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). However, after multiple-dose administration of sirolimus given 4 hours after Neoral® in renal post-transplant patients over 6 months, cyclosporine oral-dose clearance was reduced, and lower doses of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) were needed to maintain target cyclosporine concentration.

In a multiple-dose study in 150 psoriasis patients, sirolimus 0.5, 1.5, and 3 mg/m²/day was administered simultaneously with Sandimmune® Oral Solution (cyclosporine Oral Solution) 1.25 mg/kg/day. The increase in average sirolimus trough concentrations ranged between 67% to 86% relative to when Rapamune was administered without cyclosporine. The intersubject variability (% CV) for sirolimus trough concentrations ranged from 39.7% to 68.7%. There was no significant effect of multiple-dose sirolimus on cyclosporine trough concentrations following Sandimmune® Oral Solution (cyclosporine oral solution) administration. However, the % CV was higher (range 85.9% - 165%) than those from previous studies.

Diltiazem: Diltiazem is a substrate and inhibitor of CYP3A4 and P-gp; sirolimus concentrations should be monitored and a dose adjustment may be necessary [see *Drug Interactions (7.4)*]. The simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly affected the bioavailability of sirolimus. Sirolimus C_{max} , t_{max} , and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyl diltiazem and desmethyl diltiazem.

Erythromycin: Erythromycin is a substrate and inhibitor of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and erythromycin is not recommended [see *Warnings and Precautions (5.17), Drug Interactions (7.2)*]. The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 800 mg q 8h of erythromycin as erythromycin ethylsuccinate tablets at steady state to 24 healthy volunteers significantly affected the bioavailability of sirolimus and erythromycin. Sirolimus C_{max} and AUC were increased 4.4- and 4.2-fold respectively and t_{max} was increased by 0.4 hr. Erythromycin C_{max} and AUC were increased 1.6- and 1.7-fold, respectively, and t_{max} was increased by 0.3 hr.

Ketoconazole: Ketoconazole is a strong inhibitor of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and ketoconazole is not recommended [see *Warnings and Precautions (5.17), Drug Interactions (7.2)*]. Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of Rapamune Oral Solution, as reflected by increases in sirolimus C_{max} , t_{max} , and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose sirolimus did not affect steady-state 12-hour plasma ketoconazole concentrations.

Rifampin: Rifampin is a strong inducer of CYP3A4 and P-gp; co-administration of Rapamune oral solution or tablets and rifampin is not recommended. In patients where rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered [see *Warnings and Precautions (5.17), Drug Interactions (7.2)*]. Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 14 days, followed by a single 20-mg dose of sirolimus oral solution, greatly decreased sirolimus AUC and C_{max} by about 82% and 71%, respectively.

Verapamil: Verapamil is a substrate and inhibitor of CYP3A4 and P-gp; sirolimus concentrations should be monitored and a dose adjustment may be necessary; [see *Drug Interactions (7.4)*]. The simultaneous oral administration of 2 mg daily of sirolimus oral solution and 180 mg q 12h of verapamil at steady state to 26 healthy volunteers significantly affected the bioavailability of sirolimus and verapamil. Sirolimus C_{max} and AUC were increased 2.3- and 2.2-fold, respectively, without substantial change in t_{max} . The C_{max} and AUC of the pharmacologically active S(-) enantiomer of verapamil were both increased 1.5-fold and t_{max} was decreased by 1.2 hr.

Drugs Which May Be Co-administered Without Dose Adjustment

Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below. Sirolimus and these drugs may be co-administered without dose adjustments.

Acyclovir

Atorvastatin

Digoxin

Glyburide

Nifedipine

Norgestrel/ethinyl estradiol (Lo/Ovral®)

Prednisolone

Sulfamethoxazole/trimethoprim (Bactrim®)

Other Drug-Drug Interactions

Co-administration of Rapamune with other known strong inhibitors of CYP3A4 and/or P-gp (such as voriconazole, itraconazole, telithromycin, or clarithromycin) or other known strong inducers of CYP3A4 and/or P-gp (such as rifabutin) is not recommended [see *Warnings and Precautions (5.17), Drug Interactions (7.2)*]. In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered.

Care should be exercised when drugs or other substances that are substrates and/or inhibitors or inducers of CYP3A4 are administered concomitantly with Rapamune. Other drugs that have the potential to increase sirolimus blood concentrations include (but are not limited to):

Calcium channel blockers: nicardipine.

Antifungal agents: clotrimazole, fluconazole.

Antibiotics: troleandomycin.

Gastrointestinal prokinetic agents: cisapride, metoclopramide.

Other drugs: bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir).

Other drugs that have the potential to decrease sirolimus concentrations include (but are not limited to):

Anticonvulsants: carbamazepine, phenobarbital, phenytoin.

Antibiotics: rifapentine.

Other Drug-Food Interactions

Grapefruit juice reduces CYP3A4-mediated drug metabolism. Grapefruit juice must not be taken with or used for dilution of Rapamune [see *Dosage and Administration (2.7), Drug Interactions (7.3)*].

Drug-Herb Interactions

St. John's Wort (*hypericum perforatum*) induces CYP3A4 and P-gp. Since sirolimus is a substrate for both cytochrome CYP3A4 and P-gp, there is the potential that the use of St. John's Wort in patients receiving Rapamune could result in reduced sirolimus concentrations [see *Drug Interactions (7.4)*].

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at sirolimus doses 30 to 120 times higher than the 2 mg daily clinical dose (adjusted for body

surface area), there was a statistically significant increase in malignant lymphoma at all dose levels compared with controls. In a second mouse study at dosages that were approximately 3 to 16 times the clinical dose (adjusted for body surface area), hepatocellular adenoma and carcinoma in males were considered sirolimus-related. In the 104-week rat study at dosages equal to or lower than the clinical dose of 2 mg daily (adjusted for body surface area), there were no significant findings.

Sirolimus was not genotoxic in the *in vitro* bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the *in vivo* mouse micronucleus assay.

Fertility was diminished slightly in both male and female rats following oral administration of sirolimus at doses approximately 10 times or 2 times, respectively, the clinical dose of 2 mg daily (adjusted for body surface area). In male rats, atrophy of testes, epididymides, prostate, seminiferous tubules and/or reduction in sperm counts were observed. In female rats, reduced size of ovaries and uterus was observed. Reduction of sperm count in male rats was reversible upon cessation of dosing in one study. Testicular tubular degeneration was also seen in a 4-week intravenous study of sirolimus in monkeys at doses that were approximately equal to the clinical dose (adjusted for body surface area).

14 CLINICAL STUDIES

14.1 Prophylaxis of Organ Rejection

Rapamune Oral Solution

The safety and efficacy of Rapamune Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials. These studies compared two dose levels of Rapamune Oral Solution (2 mg and 5 mg, once daily) with azathioprine (Study 1) or placebo (Study 2) when administered in combination with cyclosporine and corticosteroids. Study 1 was conducted in the United States at 38 sites. Seven hundred nineteen (719) patients were enrolled in this trial and randomized following transplantation; 284 were randomized to receive Rapamune Oral Solution 2 mg/day; 274 were randomized to receive Rapamune Oral Solution 5 mg/day, and 161 to receive azathioprine 2-3 mg/kg/day. Study 2 was conducted in Australia, Canada, Europe, and the United States, at a total of 34 sites. Five hundred seventy-six (576) patients were enrolled in this trial and randomized before transplantation; 227 were randomized to receive Rapamune Oral Solution 2 mg/day; 219 were randomized to receive Rapamune Oral Solution 5 mg/day, and 130 to receive placebo. In both studies, the use of antilymphocyte antibody induction therapy was prohibited. In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The tables below summarize the results of the primary efficacy analyses from these trials. Rapamune Oral Solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure (statistically significant at the < 0.025 level; nominal significance

level adjusted for multiple [2] dose comparisons) at 6 months following transplantation compared with both azathioprine and placebo.

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 24 MONTHS FOR STUDY 1^{a,b}

Parameter	Rapamune Oral Solution 2 mg/day (n = 284)	Rapamune Oral Solution 5 mg/day (n = 274)	Azathioprine 2-3 mg/kg/day (n = 161)
Efficacy failure at 6 months^c	18.7	16.8	32.3
<i>Components of efficacy failure</i>			
Biopsy-proven acute rejection	16.5	11.3	29.2
Graft loss	1.1	2.9	2.5
Death	0.7	1.8	0
Lost to follow-up	0.4	0.7	0.6
Efficacy failure at 24 months	32.8	25.9	36.0
<i>Components of efficacy failure</i>			
Biopsy-proven acute rejection	23.6	17.5	32.3
Graft loss	3.9	4.7	3.1
Death	4.2	3.3	0
Lost to follow-up	1.1	0.4	0.6

a: Patients received cyclosporine and corticosteroids.

b: Includes patients who prematurely discontinued treatment.

c: Primary endpoint.

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 36 MONTHS FOR STUDY 2^{a,b}

Parameter	Rapamune Oral Solution 2 mg/day (n = 227)	Rapamune Oral Solution 5 mg/day (n = 219)	Placebo (n = 130)
Efficacy failure at 6 months^c	30.0	25.6	47.7
<i>Components of efficacy failure</i>			
Biopsy-proven acute rejection	24.7	19.2	41.5
Graft loss	3.1	3.7	3.9
Death	2.2	2.7	2.3
Lost to follow-up	0	0	0
Efficacy failure at 36 months	44.1	41.6	54.6
<i>Components of efficacy failure</i>			
Biopsy-proven acute rejection	32.2	27.4	43.9
Graft loss	6.2	7.3	4.6
Death	5.7	5.9	5.4
Lost to follow-up	0	0.9	0.8

a: Patients received cyclosporine and corticosteroids.

b: Includes patients who prematurely discontinued treatment.

c: Primary endpoint.

Patient and graft survival at 1 year were co-primary endpoints. The following table shows graft and patient survival at 1 and 2 years in Study 1, and 1 and 3 years in Study 2. The graft and patient survival rates were similar in patients treated with Rapamune and comparator-treated patients.

GRAFT AND PATIENT SURVIVAL (%) FOR STUDY 1 (12 AND 24 MONTHS) AND STUDY 2 (12 AND 36 MONTHS)^{a,b}

Parameter	Rapamune Oral Solution 2 mg/day	Rapamune Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1	(n = 284)	(n = 274)	(n = 161)	
Graft survival				
Month 12	94.7	92.7	93.8	
Month 24	85.2	89.1	90.1	
Patient survival				
Month 12	97.2	96.0	98.1	
Month 24	92.6	94.9	96.3	
Study 2	(n = 227)	(n = 219)	.	(n = 130)
Graft survival				
Month 12	89.9	90.9	87.7	
Month 36	81.1	79.9	80.8	
Patient survival				
Month 12	96.5	95.0	94.6	
Month 36	90.3	89.5	90.8	

a: Patients received cyclosporine and corticosteroids.

b: Includes patients who prematurely discontinued treatment.

The reduction in the incidence of first biopsy-confirmed acute rejection episodes in patients treated with Rapamune compared with the control groups included a reduction in all grades of rejection.

In Study 1, which was prospectively stratified by race within center, efficacy failure was similar for Rapamune Oral Solution 2 mg/day and lower for Rapamune Oral Solution 5 mg/day compared with azathioprine in Black patients. In Study 2, which was not prospectively stratified by race, efficacy failure was similar for both Rapamune Oral Solution doses compared with placebo in Black patients. The decision to use the higher dose of Rapamune Oral Solution in Black patients must be weighed against the increased risk of dose-dependent adverse events that were observed with the Rapamune Oral Solution 5-mg dose [see *Adverse Reactions (6.1)*].

PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS^{a,b}

Parameter	Rapamune Oral Solution 2 mg/day	Rapamune Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1				
Black (n = 166)	34.9 (n = 63)	18.0 (n = 61)	33.3 (n = 42)	
Non-Black (n = 553)	14.0 (n = 221)	16.4 (n = 213)	31.9 (n = 119)	
Study 2				
Black (n = 66)	30.8 (n = 26)	33.7 (n = 27)		38.5 (n = 13)
Non-Black (n = 510)	29.9 (n = 201)	24.5 (n = 192)		48.7 (n = 117)

a: Patients received cyclosporine and corticosteroids.

b: Includes patients who prematurely discontinued treatment.

Mean glomerular filtration rates (GFR) post-transplant were calculated by using the Nankivell equation at 12 and 24 months for Study 1, and 12 and 36 months for Study 2. Mean GFR was lower in patients treated with cyclosporine and Rapamune Oral Solution compared with those treated with cyclosporine and the respective azathioprine or placebo control.

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (Mean \pm SEM, cc/min) BY NANKIVELL EQUATION POST-TRANSPLANT^{a,b}

Parameter	Rapamune Oral Solution 2 mg/day	Rapamune Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1				
Month 12	57.4 \pm 1.3 (n = 269)	54.6 \pm 1.3 (n = 248)	64.1 \pm 1.6 (n = 149)	
Month 24	58.4 \pm 1.5 (n = 221)	52.6 \pm 1.5 (n = 222)	62.4 \pm 1.9 (n = 132)	
Study 2				
Month 12	52.4 \pm 1.5 (n = 211)	51.5 \pm 1.5 (n = 199)		58.0 \pm 2.1 (n = 117)
Month 36	48.1 \pm 1.8 (n = 183)	46.1 \pm 2.0 (n = 177)		53.4 \pm 2.7 (n = 102)

a: Includes patients who prematurely discontinued treatment.

b: Patients who had a graft loss were included in the analysis with GFR set to 0.0.

Within each treatment group in Studies 1 and 2, mean GFR at one-year post-transplant was lower in patients who experienced at least one episode of biopsy-proven acute rejection, compared with those who did not.

Renal function should be monitored, and appropriate adjustment of the immunosuppressive regimen should be considered in patients with elevated or increasing serum creatinine levels [see *Warnings and Precautions* (5.8)].

Rapamune Tablets

The safety and efficacy of Rapamune Oral Solution and Rapamune Tablets for the prevention of organ rejection following renal transplantation were demonstrated to be clinically equivalent in a randomized, multicenter, controlled trial [see *Clinical Pharmacology (12.3)*].

14.2 Cyclosporine Withdrawal Study

The safety and efficacy of Rapamune as a maintenance regimen were assessed following cyclosporine withdrawal at 3 to 4 months after renal transplantation. Study 3 was a randomized, multicenter, controlled trial conducted at 57 centers in Australia, Canada, and Europe. Five hundred twenty-five (525) patients were enrolled. All patients in this study received the tablet formulation. This study compared patients who were administered Rapamune, cyclosporine, and corticosteroids continuously with patients who received this same standardized therapy for the first 3 months after transplantation (pre-randomization period) followed by the withdrawal of cyclosporine. During cyclosporine withdrawal, the Rapamune dosages were adjusted to achieve targeted sirolimus whole blood trough concentration ranges (16 to 24 ng/mL until month 12, then 12 to 20 ng/mL thereafter, expressed as chromatographic assay values). At 3 months, 430 patients were equally randomized to either continue Rapamune with cyclosporine therapy or to receive Rapamune as a maintenance regimen following cyclosporine withdrawal.

Eligibility for randomization included no Banff Grade 3 acute rejection or vascular rejection episode in the 4 weeks before random assignment, serum creatinine ≤ 4.5 mg/dL, and adequate renal function to support cyclosporine withdrawal (in the opinion of the investigator). The primary efficacy endpoint was graft survival at 12 months after transplantation. Secondary efficacy endpoints were the rate of biopsy-confirmed acute rejection, patient survival, incidence of efficacy failure (defined as the first occurrence of either biopsy-proven acute rejection, graft loss, or death), and treatment failure (defined as the first occurrence of either discontinuation, acute rejection, graft loss, or death).

The following table summarizes the resulting graft and patient survival at 12, 24, and 36 months for this trial. At 12, 24, and 36 months, graft and patient survival were similar for both groups.

GRAFT AND PATIENT SURVIVAL (%): STUDY 3^a

Parameter	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Graft Survival		
Month 12 ^b	95.3 ^c	97.2
Month 24	91.6	94.0
Month 36 ^d	87.0	91.6
Patient Survival		
Month 12	97.2	98.1
Month 24	94.4	95.8
Month 36 ^d	91.6	94.0

a: Includes patients who prematurely discontinued treatment.

b: Primary efficacy endpoint.

c: Survival including loss to follow-up as an event.

d: Initial planned duration of the study.

The following table summarizes the results of first biopsy-proven acute rejection at 12 and 36 months. There was a significant difference in first biopsy-proven rejection rates between the two groups after randomization and through 12 months. Most of the post-randomization acute rejections occurred in the first 3 months following randomization.

INCIDENCE OF FIRST BIOPSY-PROVEN ACUTE REJECTION (%) BY TREATMENT GROUP AT 36 MONTHS: STUDY 3^{a,b}

Period	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Pre-randomization ^c	9.3	10.2
Post-randomization through 12 months ^c	4.2	9.8
Post-randomization from 12 to 36 months	1.4	0.5
Post-randomization through 36 months	5.6	10.2
Total at 36 months	14.9	20.5

a: Includes patients who prematurely discontinued treatment.

b: All patients received corticosteroids.

c: Randomization occurred at 3 months \pm 2 weeks.

Patients receiving renal allografts with ≥ 4 HLA mismatches experienced significantly higher rates of acute rejection following randomization to the cyclosporine withdrawal group, compared with patients who continued cyclosporine (15.3% vs. 3.0%). Patients receiving renal allografts with ≤ 3 HLA mismatches demonstrated similar rates of acute rejection between treatment groups (6.8% vs. 7.7%) following randomization.

The following table summarizes the mean calculated GFR in Study 3 (cyclosporine withdrawal study).

CALCULATED GLOMERULAR FILTRATION RATES (mL/min) BY NANKIVELL EQUATION AT 12, 24, AND 36 MONTHS POST-TRANSPLANT: STUDY 3^{a,b,c}

Parameter	Rapamune with Cyclosporine Therapy	Rapamune Following Cyclosporine Withdrawal
Month 12		
Mean \pm SEM	53.2 \pm 1.5 (n = 208)	59.3 \pm 1.5 (n = 203)
Month 24		
Mean \pm SEM	48.4 \pm 1.7 (n = 203)	58.4 \pm 1.6 (n = 201)
Month 36		
Mean \pm SEM	47.0 \pm 1.8 (n = 196)	58.5 \pm 1.9 (n = 199)

a: Includes patients who prematurely discontinued treatment.

b: Patients who had a graft loss were included in the analysis and had their GFR set to 0.0.

c: All patients received corticosteroids.

The mean GFR at 12, 24, and 36 months, calculated by the Nankivell equation, was significantly higher for patients receiving Rapamune as a maintenance regimen following cyclosporine withdrawal than for those in the Rapamune with cyclosporine therapy group. Patients who had an acute rejection prior to randomization had a significantly higher GFR following cyclosporine withdrawal compared to those in the Rapamune with cyclosporine group. There was no significant difference in GFR between groups for patients who experienced acute rejection post-randomization.

Although the initial protocol was designed for 36 months, there was a subsequent amendment to extend this study. The results for the cyclosporine withdrawal group at months 48 and 60 were consistent with the results at month 36. Fifty-two percent (112/215) of the patients in the Rapamune with cyclosporine withdrawal group remained on therapy to month 60 and showed sustained GFR.

14.3 High-Immunologic Risk Patients

Rapamune was studied in a one-year, clinical trial in high risk patients (Study 4) who were defined as Black transplant recipients and/or repeat renal transplant recipients who lost a previous allograft for immunologic reasons and/or patients with high panel-reactive antibodies (PRA; peak PRA level > 80%). Patients received concentration-controlled sirolimus and cyclosporine (MODIFIED), and corticosteroids per local practice. The Rapamune dose was adjusted to achieve target whole blood trough sirolimus concentrations of 10-15 ng/mL (chromatographic method) throughout the 12-month study period. The cyclosporine dose was adjusted to achieve target whole blood trough concentrations of 200-300 ng/mL through week 2, 150-200 ng/mL from week 2 to week 26, and 100-150 ng/mL from week 26 to week 52 [see *Clinical Pharmacology (12.3)*] for the observed trough concentrations ranges. Antibody

induction was allowed per protocol as prospectively defined at each transplant center, and was used in 88.4% of patients. The study was conducted at 35 centers in the United States. A total of 224 patients received a transplant and at least one dose of sirolimus and cyclosporine and was comprised of 77.2% Black patients, 24.1% repeat renal transplant recipients, and 13.5% patients with high PRA. Efficacy was assessed with the following endpoints, measured at 12 months: efficacy failure (defined as the first occurrence of biopsy-confirmed acute rejection, graft loss, or death), first occurrence of graft loss or death, and renal function as measured by the calculated GFR using the Nankivell formula. The table below summarizes the result of these endpoints.

**EFFICACY FAILURE, GRAFT LOSS OR DEATH AND CALCULATED
GLOMERULAR FUNCTION RATES (mL/min) BY NANKIVELL EQUATION AT 12
MONTHS POST-TRANSPLANT: STUDY 4**

Parameter	Rapamune with Cyclosporine, Corticosteroids (n = 224)
Efficacy Failure (%)	23.2
Graft Loss or Death (%)	9.8
Renal Function (mean \pm SEM) ^{a,b}	52.6 \pm 1.6 (n = 222)

a: Calculated glomerular filtration rate by Nankivell equation.

b: Patients who had graft loss were included in this analysis with GFR set to 0.

Patient survival at 12 months was 94.6%. The incidence of biopsy-confirmed acute rejection was 17.4% and the majority of the episodes of acute rejection were mild in severity.

14.4 Conversion from Calcineurin Inhibitors to Rapamune in Maintenance Renal Transplant Patients

Conversion from calcineurin inhibitors (CNI) to Rapamune was assessed in maintenance renal transplant patients 6 months to 10 years post-transplant (Study 5). This study was a randomized, multicenter, controlled trial conducted at 111 centers globally, including US and Europe, and was intended to show that renal function was improved by conversion from CNI to Rapamune. Eight hundred thirty (830) patients were enrolled and stratified by baseline calculated glomerular filtration rate (GFR, 20-40 mL/min vs. greater than 40 mL/min). In this trial there was no benefit associated with conversion with regard to improvement in renal function and a greater incidence of proteinuria in the Rapamune conversion arm. In addition, enrollment of patients with baseline calculated GFR less than 40 mL/min was discontinued due to a higher rate of serious adverse events, including pneumonia, acute rejection, graft loss and death [see *Adverse Reactions (6.4)*].

This study compared renal transplant patients (6-120 months after transplantation) who were converted from calcineurin inhibitors to Rapamune, with patients who continued to receive calcineurin inhibitors. Concomitant immunosuppressive medications included mycophenolate mofetil (MMF), azathioprine (AZA), and corticosteroids. Rapamune was initiated with a single loading dose of 12-20 mg, after which dosing was adjusted to achieve a target sirolimus whole

blood trough concentration of 8-20 ng/mL (chromatographic method). The efficacy endpoint was calculated GFR at 12 months post-randomization. Additional endpoints included biopsy-confirmed acute rejection, graft loss, and death. Findings in the patient stratum with baseline calculated GFR greater than 40 mL/min (Rapamune conversion, n = 497; CNI continuation, n = 246) are summarized below: There was no clinically or statistically significant improvement in Nankivell GFR compared to baseline.

**RENAL FUNCTION IN STABLE RENAL TRANSPLANT PATIENTS IN PATIENTS
WITH BASELINE GFR > 40 mL/min THE RAPAMUNE CONVERSION STUDY
(STUDY 5)**

Parameter	Rapamune conversion N=496	CNI continuation N=245	Difference (95% CI)
GFR mL/min (Nankivell) at 1 year	59.0	57.7	1.3 (-1.1, 3.7)
GFR mL/min (Nankivell) at 2 year	53.7	52.1	1.6 (-1.4, 4.6)

The rates of acute rejection, graft loss, and death were similar at 1 and 2 years. Treatment-emergent adverse events occurred more frequently during the first 6 months after Rapamune conversion. The rates of pneumonia were significantly higher for the sirolimus conversion group.

While the mean and median values for urinary protein to creatinine ratio were similar between treatment groups at baseline, significantly higher mean and median levels of urinary protein excretion were seen in the Rapamune conversion arm at 1 year and at 2 years, as shown in the table below [see *Warnings and Precautions (5.9)*]. In addition, when compared to patients who continued to receive calcineurin inhibitors, a higher percentage of patients had urinary protein to creatinine ratios > 1 at 1 and 2 years after sirolimus conversion. This difference was seen in both patients who had a urinary protein to creatinine ratio ≤ 1 and those who had a protein to creatinine ratio > 1 at baseline. More patients in the sirolimus conversion group developed nephrotic range proteinuria, as defined by a urinary protein to creatinine ratio > 3.5 (46/482 [9.5%] vs. 9/239 [3.8%]), even when the patients with baseline nephrotic range proteinuria were excluded. The rate of nephrotic range proteinuria was significantly higher in the sirolimus conversion group compared to the calcineurin inhibitor continuation group with baseline urinary protein to creatinine ratio > 1 (13/29 vs. 1/14), excluding patients with baseline nephrotic range proteinuria.

MEAN AND MEDIAN VALUES FOR URINARY PROTEIN TO CREATININE RATIO (mg/mg) BETWEEN TREATMENT GROUPS AT BASELINE, 1 AND 2 YEARS IN THE STRATUM WITH BASELINE CALCULATED GFR > 40 mL/min

Study period	Sirolimus Conversion			CNI Continuation			
	N	Mean \pm SD	Median	N	Mean \pm SD	Median	p-value
Baseline	410	0.35 \pm 0.76	0.13	207	0.28 \pm 0.61	0.11	0.381
1 year	423	0.88 \pm 1.61	0.31	203	0.37 \pm 0.88	0.14	<0.001
2 years	373	0.86 \pm 1.48	0.32	190	0.47 \pm 0.98	0.13	<0.001

The above information should be taken into account when considering conversion from calcineurin inhibitors to Rapamune in stable renal transplant patients due to the lack of evidence showing that renal function improves following conversion, and the finding of a greater increment in urinary protein excretion, and an increased incidence of treatment-emergent nephrotic range proteinuria following conversion to Rapamune. This was particularly true among patients with existing abnormal urinary protein excretion prior to conversion.

14.5 Conversion from a CNI-based Regimen to a Sirolimus-based Regimen in Liver Transplant Patients

Conversion from a CNI-based regimen to a Rapamune-based regimen was assessed in stable liver transplant patients 6-144 months post-transplant. The clinical study was a 2:1 randomized, multi-center, controlled trial conducted at 82 centers globally, including the US and Europe, and was intended to show that renal function was improved by conversion from a CNI to Rapamune without adversely impacting efficacy or safety. A total of 607 patients were enrolled.

The study failed to demonstrate superiority of conversion to a Rapamune-based regimen compared to continuation of a CNI-based regimen in baseline-adjusted GFR, as estimated by Cockcroft-Gault, at 12 months (62 mL/min in the Rapamune conversion group and 63 mL/min in the CNI continuation group). The study also failed to demonstrate non-inferiority, with respect to the composite endpoint consisting of graft loss and death (including patients with missing survival data) in the Rapamune conversion group compared to the CNI continuation group (6.6% versus 5.6%). The number of deaths in the Rapamune conversion group (15/393, 3.8%) was higher than in the CNI continuation group (3/214, 1.4%), although the difference was not statistically significant. The rates of premature study discontinuation (primarily due to adverse events or lack of efficacy), adverse events overall (infections, specifically), and biopsy-proven acute liver graft rejection at 12 months were all significantly greater in the Rapamune conversion group compared to the CNI continuation group.

14.6 Pediatrics

Rapamune was evaluated in a 36-month, open-label, randomized, controlled clinical trial at 14 North American centers in pediatric (aged 3 to < 18 years) renal transplant patients considered to be at high-immunologic risk for developing chronic allograft nephropathy, defined as a

history of one or more acute allograft rejection episodes and/or the presence of chronic allograft nephropathy on a renal biopsy. Seventy-eight (78) subjects were randomized in a 2:1 ratio to Rapamune (sirolimus target concentrations of 5 to 15 ng/mL, by chromatographic assay, n = 53) in combination with a calcineurin inhibitor and corticosteroids or to continue calcineurin-inhibitor-based immunosuppressive therapy (n = 25). The primary endpoint of the study was efficacy failure as defined by the first occurrence of biopsy-confirmed acute rejection, graft loss, or death, and the trial was designed to show superiority of Rapamune added to a calcineurin-inhibitor-based immunosuppressive regimen compared to a calcineurin-inhibitor-based regimen. The cumulative incidence of efficacy failure up to 36 months was 45.3% in the Rapamune group compared to 44.0% in the control group, and did not demonstrate superiority. There was one death in each group. The use of Rapamune in combination with calcineurin inhibitors and corticosteroids was associated with an increased risk of deterioration of renal function, serum lipid abnormalities (including, but not limited to, increased serum triglycerides and cholesterol), and urinary tract infections [see *Warnings and Precautions* (5.8)]. This study does not support the addition of Rapamune to calcineurin-inhibitor-based immunosuppressive therapy in this subpopulation of pediatric renal transplant patients.

15 REFERENCES

Clinical Therapeutics, Volume 22, Supplement B, April 2000 [see *Dosage and Administration* (2.3)].

16 HOW SUPPLIED/STORAGE AND HANDLING

Since Rapamune is not absorbed through the skin, there are no special precautions. However, if direct contact with the skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes with plain water.

16.1 Rapamune Oral Solution

Each Rapamune Oral Solution carton, NDC 0008-1030-06, contains one 2 oz (60 mL fill) amber glass bottle of sirolimus (concentration of 1 mg/mL), one oral syringe adapter for fitting into the neck of the bottle, sufficient disposable amber oral syringes and caps for daily dosing, and a carrying case.

Rapamune Oral Solution bottles should be stored protected from light and refrigerated at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, the contents should be used within one month. If necessary, the patient may store the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., not more than 15 days for the bottles).

An amber syringe and cap are provided for dosing, and the product may be kept in the syringe for a maximum of 24 hours at room temperatures up to 25°C (77°F) or refrigerated at 2°C to 8°C (36°F to 46°F). The syringe should be discarded after one use. After dilution, the preparation should be used immediately.

Rapamune Oral Solution provided in bottles may develop a slight haze when refrigerated. If such a haze occurs, allow the product to stand at room temperature and shake gently until the haze disappears. The presence of this haze does not affect the quality of the product.

16.2 Rapamune Tablets

Rapamune Tablets are available as follows:

- NDC 0008-1041-05, 1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side; bottle containing 100 tablets.
- NDC 0008-1041-10, 1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side; in Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each).
- NDC 0008-1042-05, 2 mg, yellow-to-beige triangular-shaped tablets marked "RAPAMUNE 2 mg" on one side; bottle containing 100 tablets.

Rapamune Tablets should be stored at 20° to 25°C [USP Controlled Room Temperature] (68° to 77°F). Use cartons to protect blister cards and strips from light. Dispense in a tight, light-resistant container as defined in the USP.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.4).

17.1 Dosage

Patients should be given complete dosage instructions [see *Patient Counseling Information (17.4)*].

17.2 Skin Cancer Events

Patients should be told that exposure to sunlight and ultraviolet (UV) light should be limited by wearing protective clothing and using a sunscreen with a high protection factor because of the increased risk for skin cancer [see *Warnings and Precautions (5.15)*].

17.3 Pregnancy Risks

Women of childbearing potential should be informed of the potential risks during pregnancy and told that they should use effective contraception prior to initiation of Rapamune therapy, during Rapamune therapy, and for 12 weeks after Rapamune therapy has been stopped [see *Use in Specific Populations (8.1)*].

17.4 FDA-Approved Patient Labeling

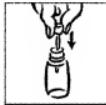
PATIENT INSTRUCTIONS FOR RAPAMUNE (SIROLIMUS) ORAL SOLUTION

Bottles

1. Open the solution bottle. Remove the safety cap by squeezing the tabs on the cap and twisting counterclockwise.



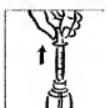
2. On first use, insert the adapter assembly (plastic tube with stopper) tightly into the bottle until it is even with the top of the bottle. Do not remove the adapter assembly from the bottle once inserted.



3. For each use, tightly insert one of the amber syringes with the plunger fully depressed into the opening in the adapter.



4. Withdraw the prescribed amount of Rapamune Oral Solution by gently pulling out the plunger of the syringe until the bottom of the black line of the plunger is even with the appropriate mark on the syringe. Always keep the bottle in an upright position. If bubbles form in the syringe, empty the syringe into the bottle and repeat the procedure.



5. You may have been instructed to carry your medication with you. If it is necessary to carry the filled syringe, place a cap securely on the syringe – the cap should snap into place.



6. Then place the capped syringe in the enclosed carrying case. Once in the syringe, the medication may be kept at room temperature or refrigerated and should be used within 24 hours. Extreme temperatures (below 36°F and above 86°F) should be avoided. Remember to keep this medication out of the reach of children.



7. Empty the syringe into a glass or plastic cup containing at least 2 ounces (1/4 cup, 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup, 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice, or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune Oral Solution. The syringe and cap should be used once and then discarded.



8. Always store the bottles of medication in the refrigerator. When refrigerated, a slight haze may develop in the solution. The presence of a haze does not affect the quality of the product. If this happens, bring the Rapamune Oral Solution to room temperature and shake until the haze disappears. If it is necessary to wipe clean the mouth of the bottle before returning the product to the refrigerator, wipe with a dry cloth to avoid introducing water, or any other liquid, into the bottle.



US Pat. Nos.: 5,100,899; 5,212,155; 5,308,847; 5,403,833; 5,536,729; 5,989,591.

This product's label may have been updated. For current package insert and further product information, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

For Rapamune Oral Tablets:

Wyeth®

Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

For Rapamune Oral Solution:

Wyeth®

Manufactured for:
Wyeth Pharmaceuticals Inc.
Philadelphia, PA 19101

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